DOES NOT CIRCULATE

1958 Assembly — Interstate Postgraduate Medical Association — Cleveland — November 10-13

Volume 24, Number 3 **SEPTEMBER 1958**

Postgraduate Medicine

[illegible]

Special Issue

THERAPEUTICS

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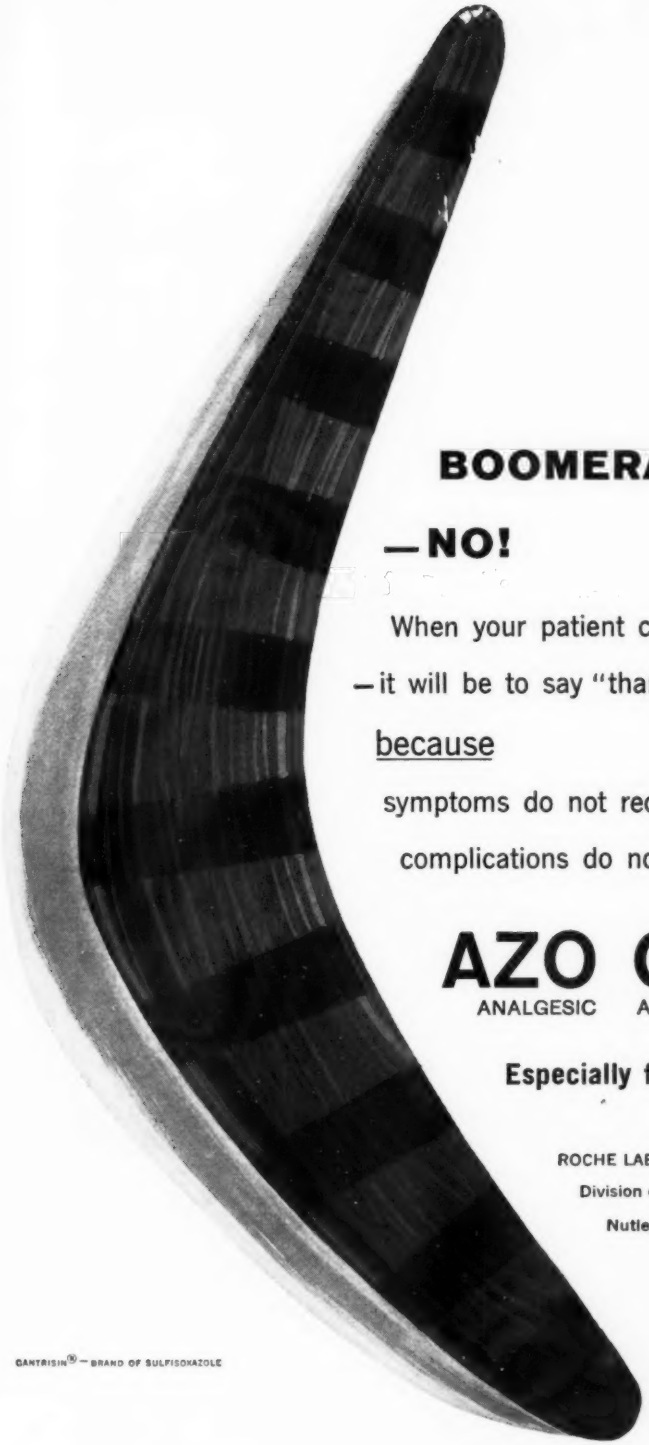

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because

symptoms do not recur—

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Especially for urinary tract infections

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• STERILITY

Q. A 27 year old woman has symptoms of anxiety, a slight intolerance to cold, anorexia, and fullness in the thyroid region. Although married for four years, she has not become pregnant.

Results of sterility studies have been negative; numerous basal metabolism tests, as well as blood studies and the determination of radioiodine uptake and cholesterol level, have been normal. The patient has received some relief from meprobamate, but the administration of thyroid extract caused nervousness and was discontinued.

What would you suggest in regard to further studies or therapy, or both?

M.D.—Puerto Rico

A. So far as can be determined from the question, the patient is normal in every respect. It is mentioned that the patient has anorexia, but nothing is said as to whether or not there is any loss of weight or any abnormality of the menstrual function.

Since the results of studies of sterility have been negative, it is presumed that the tubes are open, that biopsy of premenstrual endometrial tissues revealed progestational endometrium, that results of studies of the husband's semen are normal, and that a postcoital test has been done.

If all the foregoing measures have been taken and if the patient indeed is completely normal, there is nothing further to be done except to advise the patient in the proper technic of coitus and timing. Certainly, there seems to be no abnormality of thyroid function. If the patient is truly emotionally disturbed, a psychiatric evaluation would be in order.

• MUSCLE STRENGTH

Q. Would you explain the different factors involved in muscle strength? Which is stronger, the longer or the shorter muscle?

M.D.—Ontario

A. The strength of contraction of a skeletal muscle is determined by the contractility of the muscle fibers, the number of active muscle fibers, the frequency with which these fibers are activated, and the degree of initial stretch of the fibers. The *modus operandi* of factors which affect the contractile strength of a muscle fiber is not well understood. A decrease of this strength occurs in the presence of certain electrolyte and endocrine disturbances.

The number of active muscle fibers is determined by the number of lower motor neurons which can be activated. Each neuron controls up to several hundred muscle fibers which constitute a motor unit. Weakness can occur as the result of a decrease in the number of fibers capable of responding because of denervation or degeneration of the fibers, or failure of neuromuscular conduction or of upper motor neuron or reflex excitation of lower motor neurons.

Maximal tension occurs in a tetanic contraction when the muscle fibers are activated at a rate of about 50 times per second. Slow, or red, muscles such as the soleus reach maximal tension at lower rates of activation than do fast, or pale, muscles such as the gastrocnemius. In a voluntary contraction, greater effort increases the strength of contraction by increasing the number of active motor units and the frequency with which they are activated. Motivation and training are im-

(Continued on page A-20)

when you treat hypertensive patients

double duty RAUDIXIN

Squibb Standardized Whole Root Rauwolfia Serpentina

is the solid base line for successful therapy

Raudixin helps you relieve pressures in your patients

Raudixin "lowers blood pressure and slows the pulse rate much more efficiently than the barbiturates. . . . It is not habit-forming and is synergistic with all other known hypotensive drugs."*

Raudixin helps you relieve pressures on your patients

Raudixin "relieves anxiety and tension, particularly the tension headache of the mild hypertensive patient, better than any other drug."*

RAUDIXIN..."is the best symptom reliever."*

In mild to moderate cases, Raudixin is frequently sufficient.

Base line therapy with Raudixin permits lower dosage of more toxic agents. The incidence and side effects of these agents are minimized. Diuretics often potentiate the antihypertensive effect of Raudixin.

*Finnerty, F. A. Jr.: New York State J. Med. 57:2957 (Sept. 15) 1957.

SQUIBB CENTENNIAL 1858 1958 SQUIBB *Squibb Quality—the Priceless Ingredient*

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portant factors in this regard. The optimal length of the muscle at which contraction is maximal corresponds to the natural or resting length of that muscle in the body. The leverage afforded by the attachments of the muscle is important.

In muscles of equal weight, the greater tension will be produced by the muscle with the greater number of shorter fibers. However, the range of motion of such a muscle will be less than that of the longer muscle.

• POSTOPERATIVE FIXATION OF TESTIS

Q. Two weeks after an inguinal herniorrhaphy, a nine year old boy who had bilateral descending testes has one testis caught at the level of the external ring. Although some difficulty was experienced in maintaining the scrotal position of the testis during surgery, it was thought that time would ensure its normal position. Is immediate repair advisable, or would it be better to delay intervention for a while?

M.D.—Arizona

A. I suggest "watchful waiting" until it is certain that the stitches have been absorbed and the hernia is well healed and not recurrent. This may take as long as two months.

• STRONGYLOIDES STERCORALIS

Q. Is there a reasonably effective treatment for *Strongyloides stercoralis* infestation besides gentian violet administered orally or intravenously? Is any information available on the strongyloidicidal action of piperazine compounds?

M.D.—Mexico

A. In the past there has been no treatment of any value for infection with *S. stercoralis*. There is some question as to whether this particular roundworm causes any symptoms.

Since the piperazine types of drugs are now available, it would seem worthwhile to give a course of treatment with dithiazanine in doses of 200 mg. three times a day for one week, then to cease administering the drug for one week before giving another course of treatment. Information on this drug may be found in an article entitled "Dithiazanine, an effective broad-spectrum anthelmintic" by J. C. Swartzwelder and associates, which appeared in the *Journal of the American Medical Association*, December 21, 1957.

• NOCTURNAL LEG CRAMPS

Q. A patient has congestive heart-failure which is controlled by 0.25 mg. DIGOXIN® daily, 2 tablets of DIURIL® twice a day, 2 cc. THIOMERIN® sodium each week, and a low salt diet. He is also receiving oxygen and Amesec for advanced emphysema, and has a parkinsonian tremor of the left upper and lower extremities which is partially controlled by 25 mg. BENADRYL® hydrochloride four times a day and KEMADRIN® three times daily. However, he still has leg cramps during the night because of the constant tremors. When he was treated with radon needles for cancer of the bladder six years ago there was evidence of pernicious anemia, for which he receives 500 μg. vitamin B_{12} intramuscularly every week. Diabetes mellitus is present and under fairly good control. Transurethral resection was performed in 1956 with fair success, but was associated with an acute bout of congestive heart-failure.

What can one do further to relieve the nocturnal leg cramps? Is there any treatment for the weakness in his legs, which is especially noticeable after sitting? Is 50 mg. nicotinic acid, given three times daily, contraindicated as an antiatherosclerosis factor? He has not received any steroids.

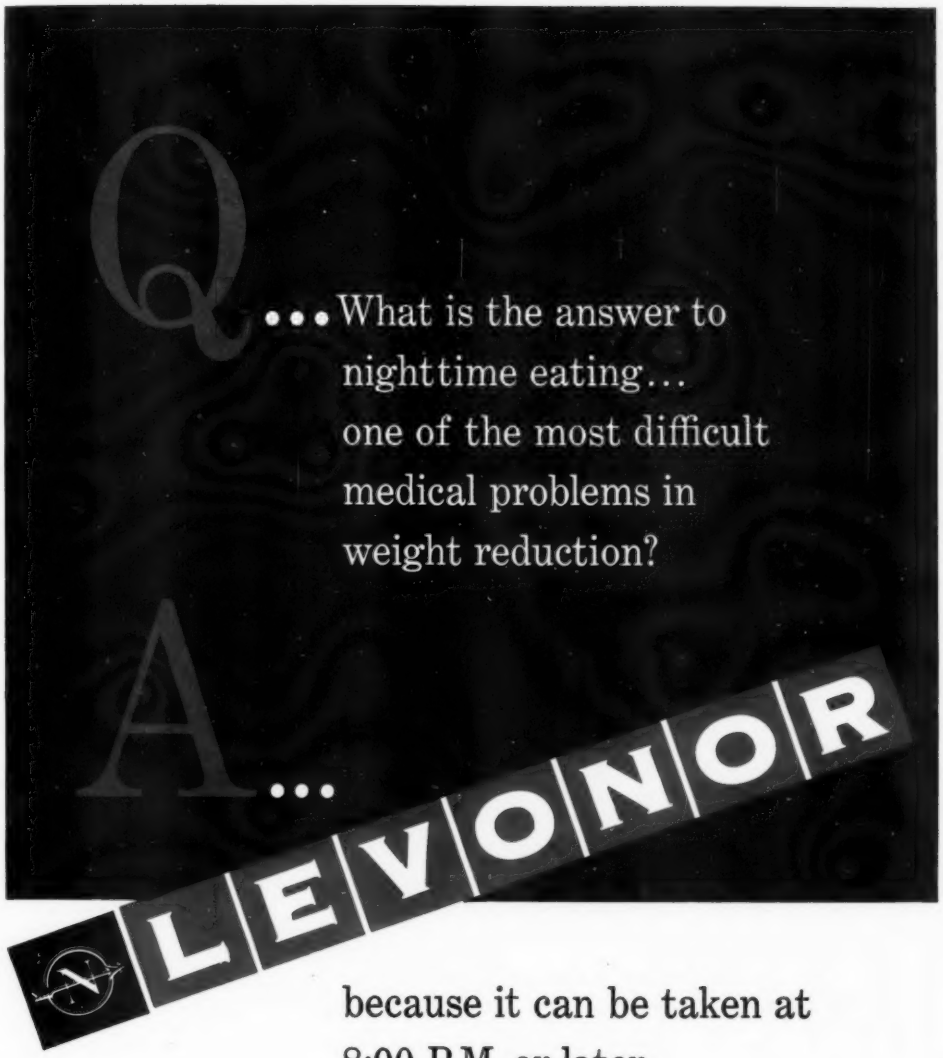
M.D.—Ontario

A The treatment of nocturnal cramps in the legs at best is only partially satisfactory. In certain instances, ingestion of 3 to 5 gr. quinine a few minutes before retiring produces abatement or cessation of the symptoms. Another medication sometimes tried is zoxazolamine (FLEXIN®), which can be administered in doses of 250 mg. at the evening meal and before retiring. The bedtime dose can be doubled if there are no untoward effects from a single tablet. There would appear to be no special contraindication to taking 50 mg. nicotinic acid three times a day; however, its prophylactic action against atherosclerosis is highly questionable.

Second Consultant: Wearing woolen stockings at night that reach above the knees has helped nocturnal leg cramps. Also, quinine sulfate taken after the evening meal and at bedtime has been helpful to some patients.

Nicotinic acid, 50 to 100 mg. three times a day, is a vasodilator and is not contraindicated in this case unless it causes too much flushing.

(Continued on page A-22)



because it can be taken at
8:00 P.M. or later
without interfering
with sleep.

administration and dosage:
Average dose: 5 to 10 mg. twice daily.

how supplied:
Bottles of 100 tablets, each tablet containing 5 mg. of
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• POLYURIA

Q. A 75 year old woman who has diabetes insipidus passes an average of 7 pt. of urine daily. She has nocturia four or five times and has poor bladder control. She can reduce urination only by denying herself fluids.

A recent urinalysis revealed the following: appearance slightly cloudy and straw-colored, pH 5, specific gravity 1.005, no albumin, and a few erythrocytes and granular casts. The patient eliminates the normal amount of solids in the urine. Blood pressure is usually moderate with only an occasional tendency to rise. About two years ago the patient had a cholecystectomy and was hospitalized for 78 days, during which time the hemoglobin and red blood cell counts were lowered and the patient lost weight.

What treatment would you advise? I am reluctant to prescribe PITRESSIN®, as it is a vasopressor.

M.D.—South Dakota

A. It is not clear that this woman has diabetes insipidus, since such patients because of uncontrollable thirst usually cannot voluntarily restrict water intake. If she actually can restrict water intake voluntarily, this, of course, is the best treatment for her.

Pitressin could cause an increase in blood pressure, but it could also precipitate angina pectoris if the patient has any significant degree of coronary atherosclerosis. Nevertheless, it is important for diagnostic purposes to see if her thirst and polyuria can be controlled by Pitressin. Therefore, I suggest that the following procedure be carried out without the patient's knowing the contents of the injections:

1. Inject 0.2 cc. aqueous Pitressin subcutaneously and measure the volume of urine excretion and specific gravity during a six hour period.

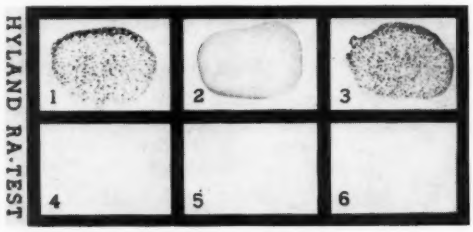
2. On another day, inject 0.2 cc. saline for placebo control and measure urine output and specific gravity during a six hour period.

3. If she responds to aqueous Pitressin and not to the placebo injection, then it will be worthwhile to give Pitressin tannate in oil in doses of 0.5 cc. every other day (the time interval varies from 24 to 96 hours in individual patients). She may need 1 cc. Note that the ampule should be thoroughly mixed by inverting it a number of times before drawing fluid into the syringe. Pitressin tannate in oil releases pitressin so slowly that hypertension and angina do not result.

RAPID SCREENING TEST FOR RHEUMATOID ARTHRITIS

RA-TEST

Trade Mark of Hyland Laboratories



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neomycin and hydrocortamate

TOPICAL OINTMENT

The extraordinary water-soluble dermatologic corticoid, MAGNACORT, combined with the outstanding topical antibiotic, neomycin, for superior control of inflammatory and/or infectious dermatoses.[1-6] Improvement or complete cure noted in 88% of a series, including many skin disorders notoriously difficult to treat.[5]

SUPPLIED: In 1/6-oz. and 1/2-oz. tubes, 0.5% neomycin sulfate and 0.5% hydrocortamate hydrochloride.

Also available: **MAGNACORT® Topical Ointment:** In 1/6-oz. and 1/2-oz. tubes, 0.5% hydrocortamate hydrochloride.

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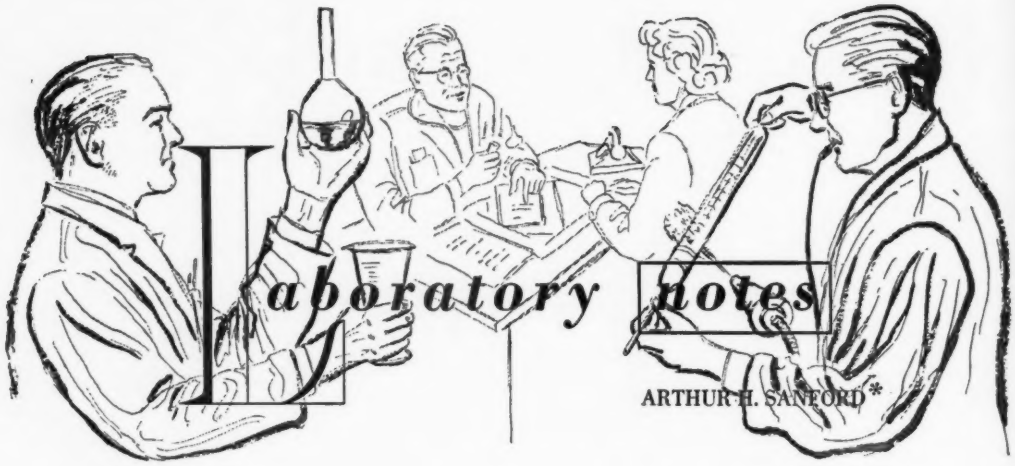

ARTHUR H. SANFORD*

Alkaline Phosphatase in the White Cells in Leukemia and Leukemoid Reactions

AN interesting article[1] on this subject appeared recently from the Department of Hematology and Pathology, Royal Infirmary and University of Manchester, England.

While the general reader of this column may not be too interested in histochemical technics, there is considerable diagnostic and prognostic significance in a study of the alkaline phosphatase content of the white cells in certain somewhat puzzling conditions, as brought out clearly by the authors.

The technic is as follows:

1. Fix the blood or marrow slide preparations for 30 seconds in 10 ml. of formalin to 90 ml. of absolute methyl alcohol.

2. Wash for a few seconds and incubate for two hours at 37° C. in a freshly prepared buffer substrate solution containing 30 ml. of 10 per cent sodium barbital, 30 ml. of 3.2 per cent sodium β-glycerophosphate, 30 ml. of M/10 magnesium sulfate, 45 ml. of 2 per cent calcium nitrate, and 165 ml. of distilled water. (This adds up to 300 ml. Stock solutions of sodium β-glycerophosphate, sodium barbital and the formalin-methyl alcohol fixative may be kept refrigerated until used.)

3. Rinse the slides for a few seconds in distilled water containing a few drops of 2 per cent calcium nitrate solution.

4. Immerse the slides in 2 per cent cobalt nitrate solution for five minutes.

5. Wash well and treat for 10 seconds in a weak solution of ammonium sulfide (about 1 ml. of ammonium sulfide to 80 ml. of water).

6. Wash well and counterstain with 2 per cent aqueous solution of safranine for 10 seconds.

7. Wash well and mount.

The authors also put through at the same time control films of normal blood and those of known high leukocyte phosphatase activity.

Black granules in the cytoplasm of neutrophils show alkaline phosphatase activity. Strongly positive cells show many coarse granules, or the whole cytoplasm may appear densely black. Phosphatase is expressed as absent, weak or strong, assessed by examining 400 consecutive neutrophil polymorphic leukocytes. Lymphocytes, monocytes, plasma cells, eosinophils and all blast cells show no activity.

In chronic myeloid leukemia and acute neutrophilic leukemia, activity is reduced or absent. In all cases of leukemoid reactions due to Hodgkin's disease, myelosclerosis, reticulosarcoma, carcinosis, polycythemia, hemolytic

(Continued on page A-30)

*Emeritus Staff, Section of Clinical Pathology, Mayo Clinic; Director of Laboratories, Rochester State Hospital, Rochester, Minnesota.

X 125,000. Electron micrograph (courtesy of RCA).

the clue is in the crystals—
more than 5 times as adsorptive as kaolin

... crystals of Claysorb*, showing the tremendous surface area for adsorption. Because of Claysorb and its great adsorptive property, POLYMAGMA Plain rapidly removes intestinal bacterial toxins and irritants. Refreshing to the taste, POLYMAGMA Plain also soothes and protects the irritated mucosa; acts quickly on a low-dose regimen to restore normal intestinal function. (For infectious diarrhea, POLYMAGMA—same formula plus dihydrostreptomycin sulfate and polymyxin B sulfate.)

Supplied: Bottles of 12 fl. oz.

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NEW, MORE EFFECTIVE ANTIDIARRHEAL

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Claysorb* (Activated Attapulgite, Wyeth) and Pectin in Alumina Gel

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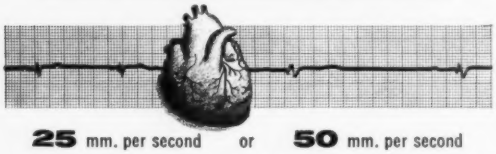
NEW design...

appearance...versatility

THE EK-III

ELECTROCARDIOGRAPH



25 mm. per second or 50 mm. per second

Whenever you need a more detailed electrocardiogram you switch the EK-III from the standard 25 mm.-per-second speed to 50 mm. This double speed enlarges horizontal dimensions of the record and rapid deflections can be more easily studied. In effect, you have a "close-up."

Weight of the unit is just 22½ lbs., yet the EK-III uses easy-to-read standard-sized record paper. The EK-III top-loading paper-drive eliminates tedious threading. Newly designed galvanometer and rigid single-tube stylus insure even greater record clarity and accuracy.

Why not write for descriptive material, or ask your dealer for a demonstration of the new Burdick electrocardiograph? We are proud to present the new dual-speed EK-III, and invite your inspection.

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anemia and tuberculosis, high levels of alkaline phosphatase in the neutrophils were found. In remission in two cases of acute lymphatic leukemia, in spite of apparent normality of the white cells, the phosphatase levels were high and remained so until fatal relapse of the leukemia.

The authors claim that this is the best means of distinguishing between myeloid leukemia and leukemoid reactions involving the myeloid series of cells.

REFERENCE

1. Leonard, B. J., Israëls, M. C. G. and Wilkinson, J. F.: Alkaline phosphatase in the white cells in leukaemia and leukaemoid reactions. Lancet 1:289-292 (February 8) 1958.

MEETINGS *and Postgraduate Courses*

American Rhinologic Society, Chicago: Fourth annual meeting, October 17-18, at the Palmer House. For further information, write to: Dr. Robert M. Hansen, 1735 North Wheeler Avenue, Portland 17, Oregon.

Columbia University Faculty of Medicine, New York: Postgraduate courses for 1958-1959:

Clinical cardiology, October 14-December 16, 1958, and February 3-April 7, 1959
Arthritis, October 23-25, 1958, and April 24-26, 1959
Ophthalmoscopy for general practitioners and pediatricians, November 6-December 4, 1958
Office proctology, November 6-7, 1958, and April 16-17, 1959
Office management of diseases of metabolism, November 14-15, 1958
Minor surgery for general practitioners, December 1-3, 1958
Common skin diseases and treatment, January 5-March 2, 1959
Recent advances in cardiovascular disease, January 26-February 6, 1959
Cerebral palsy, March 2-20, 1959
Gastroenterology, April 6-10, 1959

Information on these and other courses for both general practitioners and specialists is available from: Dean of the Faculty of Medicine, 630 West 168th Street, New York 32.

The Women's Medical Association of the City of New York: The Mary Putnam Jacobi Fellowship, offered to a graduate woman physician, either American or foreign, starts October 1, 1959. The fellowship is given for medical research, clinical investigation or postgraduate study in a special field of medicine. The first $1000 of the $2000 fellowship will be awarded at the beginning of study; the second $1000 will be given at the end of the fourth month, subject to approval of the committee. For further information, write to: Dr. Ada Chree Reid, Secretary, 118 Riverside Drive, New York.

What's happening in Medicine

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

EXERTION AND CORONARY OCCLUSION

American College of Chest Physicians:

- A study of 1,603 patients who had had a coronary occlusion showed only 2 per cent to be associated in a time sense with severe exertion. Occlusion is the end result of an arteriosclerotic process and occurs independently of external influences. Of the 1,603 attacks, 440 occurred at rest, 412 during mild activity, 142 during moderate activity, and 367 during sleep.—Dr. Arthur M. Master, Mount Sinai Hospital, New York.
- Suprasternal transaortic coronary arteriography is a simple, safe and reproducible technic for demonstrating the pathology of lesions in coronary arteriosclerosis that are responsible for significantly decreasing coronary blood flow without producing either typical alterations on the electrocardiogram or the clinical picture of angina pectoris.—Dr. William Likoff, Hahnemann Medical College, Philadelphia.
- Angina pectoris inversa is a new angina syndrome whose characteristics are opposite to those of Heberden's angina. Attacks usually occur at rest. Severe pain lasts a minute or two.—Dr. Rexford Kennamer, Cedars of Lebanon Hospital, Los Angeles.

POLIO PROTECTION BEFORE BIRTH

Society of American Bacteriologists:

- Injections of polio vaccine given pregnant women confer protection on newborn infants. Serum antibody levels showed that vaccinated mothers gave their children protection of the same magnitude and duration as those mothers who acquired a similar level of immunity through natural exposure.—Dr. Gordon C. Brown, University of Michigan, Ann Arbor.
- A virus labeled 2060 was found responsible for about one-third of cold-like illnesses in a sample population in New Orleans. At least half of another group studied had a measurable amount of antibody to the 2060 virus. This virus was first isolated in 1955 among naval recruits in the Chicago area. It is closely related to the recently discovered JH virus.—Dr. William Pelon, Tulane University of Louisiana, New Orleans.
- Evidence strongly suggests that mothers of newborn infants may be introducing organisms of diarrhea into the hospital environment. In a study of 300 mothers and their infants, it was found that 44 mothers were harboring in their intestinal tracts one of the 11 types of *Escherichia coli* known to cause diarrhea of the newborn. Three others were carrying the organisms in their vaginal tracts. Twenty babies of the carrier mothers acquired the same type of *Esch. coli* in their intestinal tracts or in their noses and throats.—Dr. Merlin L. Cooper, University of Cincinnati, Cincinnati.

Treating neurosis in general practice

American Medical Women's Association:

- Treating psychologic problems to prevent decompensation into neuroses is not as complicated as some would have us believe. The family physician can accomplish much without benefit of a specialist.—Dr. Camilla M. Anderson, Salem, Ore.

Interim results on low cholesterol diet

American Medical Association:

- A significant trend to increased life span is suggested by follow-up studies of coronary atherosclerotic patients who were on a low cholesterol, low fat diet for 12 years. Use of unsaturated, essential fatty acids as a dietary supplement to achieve normal blood lipid chemistry is recommended. Of 50 controls who were given no dietary treatment, all had died by the end of the eleventh year; of 50 patients on a low cholesterol, low fat diet, 19 were living.—Dr. Lester M. Morrison, Crenshaw Hospital, Los Angeles.
- Peritoneoscopy offers a relatively simple method of viewing the internal abdominal organs and thus of differentiating various tumor masses felt through the abdominal wall. It aids in localizing the masses and in learning their extent and character and permits taking biopsy specimens under vision from a selected site. Peritoneoscopy is not a procedure for acute abdominal conditions, but in chronic cases it frequently will prevent unnecessary or futile surgery.—Dr. Frederick Steigmann, Cook County Hospital, Chicago.
- If older, established forms of therapy do not produce improvement within 24 hours in acute attacks of childhood asthma, short-term prednisone therapy should be started. Prolonged use entails considerable risk.—Dr. Samuel J. Levin, Detroit.
- High-voltage irradiation has substituted effectively for surgery in stomal ulcers following subtotal gastrectomy. Results were satisfactory in 18 of 23 patients treated with sharply focused x-rays in doses of about 2000 r.—Dr. Everett D. Kiefer, Lahey Clinic, Boston.
- Radioisotopes have achieved 90 per cent accuracy in diagnosing right-to-left shunts in congenital heart anomalies. A tri-iodinated radiopaque medium labeled with I^{131} is introduced directly into the heart chambers or cannulated veins at the time of catheterization.—Dr. Richard H. Greenspan, University of Minnesota Medical School, Minneapolis.
- The mortality rate among 1,573 babies undergoing surgery for pyloric stenosis has been reduced to less than 1 per cent. The reduction is largely attributable to a better understanding of fluid and electrolyte problems.—Dr. William F. Pollock, Children's Hospital, Los Angeles.

Perfusion treatment for melanoma

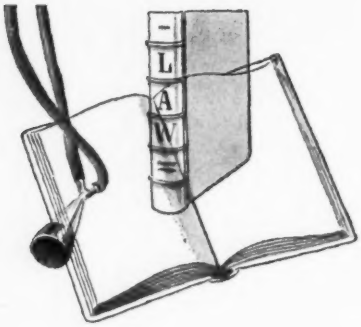
Seventh International Cancer Congress:

- Phenylalanine mustard is perfused into an isolated limb or organ to treat melanoma. A closed circulatory system in the limb uses the heart-lung machine. One patient had 175 small cancers on his leg. After three weeks, the cancers gradually faded in color, crusted and flattened, leaving only small cancer-free freckles. Seven other patients have been similarly treated.—Dr. Edward T. Krementz, Tulane University of Louisiana, New Orleans.
- Twenty-eight of 42 men with cancer of the breast benefited from castration or estrogen or adrenal hormones. Only five of the 42 patients had operable cancers when first seen.—Dr. Norman Treves, chief of breast service, Memorial Center for Cancer and Allied Diseases, New York.

failure

markedly relieves pulmonary edema

ANY INDICATION FOR DIURESIS IS AN INDICATION FOR DIURIL



Forensic Medicine

Legal Aspects of Sudden, Unexplained and Obscure Causes of Death

ROWLAND H. LONG*

Massachusetts Mutual Life Insurance Company, Springfield, Massachusetts

WHEN sudden and unexpected death occurs in a person who apparently has been in good health, the unexpectedness of the death is perhaps of greater significance than the suddenness. An unexpected occurrence is the opposite of something that is believed to be about to happen or that is looked for with some confidence.

ROWLAND H. LONG

The New York City Charter[1] provides that in the city of New York when any person in apparent good health dies suddenly, when unattended by a physician, while in prison, or in any suspicious or unusual manner, the Office of the Chief Medical Examiner shall be notified. The medical examiner must perform an autopsy if he believes it to be necessary.

In New York City the Chief Medical Examiner, a deputy or an assistant medical examiner must investigate all sudden, suspicious, unusual and violent deaths and those in which a physician has not been in attendance. The Office of the Chief Medical Examiner operates independently of other official agencies, and its investigation is in no way controlled or hindered by any other agency. The medical examiner cooperates with the law enforcement agencies. His study and opinion must be unbiased. He is an investigator, not a prosecutor or defender.

Since the enactment of the New York statute, some other jurisdictions have adopted similar laws. However, an examination of the statutes relating to coroners and medical examiners shows that in many jurisdictions provisions are made only for the investigation of obviously violent and suspicious deaths. There evidently is no recognizance that in many vio-

(Continued on page A-40)

*Vice-president and General Counsel, Massachusetts Mutual Life Insurance Company, Springfield, Massachusetts.

Presented before the tenth annual meeting of the American Academy of Forensic Sciences at Cleveland.

new

Tao*

PRONOUNCED TAY-O

(brand of triacetyloleandomycin with glycosaminol)

Capsules / Oral Suspension

designed for effective control of common gram-positive infections

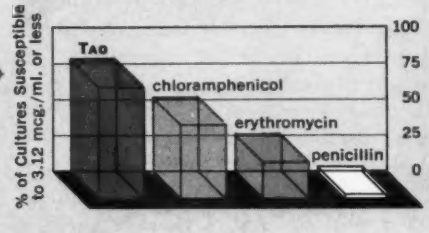
effective . . .

CLINICAL RESULTS	adults	children	all Staph infections
Cured	172 (80%)	148 (89%)	71 (88%)
Improved	28 (13%)	8 (5%)	7 (9%)
Failure	17 (7%)	11 (6%)	3 (3%)

Types of infecting organisms: The majority of identified etiologic microorganisms were Staph. aureus and Staph. albus. Tao has its greatest usefulness against organisms such as: staphylococci (including strains resistant to other antibiotics), streptococci (beta-hemolytic strains, alpha-hemolytic strains and enterococci), pneumococci, gonococci, Hemophilus influenzae.

even against resistant staph[1,2] . . .

Per cent of "antibiotic-resistant" epidemic staphylococci cultures susceptible to Tao, erythromycin, penicillin and chloramphenicol.[1]



well tolerated . . .

REACTIONS: (a) adults	(b) children
Total—9.2% (20 out of 217)	Total—0.6% (1 out of 167)
Skin rash—1.4% (3 out of 217)	Skin rash—none
Gastrointestinal—7.8% (17 out of 217)	Gastrointestinal—0.6% (1 out of 167)

There was complete freedom from adverse reactions in 94.5% of all patients. Side effects in the other 5.5% were usually mild and seldom required discontinuance of therapy.

plus . . . stability in gastric acid • rapid, high and sustained blood levels • high urinary concentrations • outstanding palatability in a liquid preparation

Dosage and Administration: Dosage varies according to the severity of the infection. For adults, the average dose is 250 mg. q.i.d.; to 500 mg. q.i.d. in more severe infections. For children 8 months to 8 years of age, a daily dose of approximately 30 mg./Kg. body weight in divided doses has been found effective. Since Tao is therapeutically stable in gastric acid, it may be administered at any time, without regard to meals.

Supplied: Tao Capsules—250 mg. and 125 mg.; bottles of 60. Tao for Oral Suspension—1.5 Gm.; 125 mg. per teaspoonful (5 cc.) when reconstituted; unusually palatable cherry flavor; 2 oz. bottle.

References: 1. English, A. R., and Fink, F. C.: Antibiotics & Chemother. (Aug.) 1958. 2. English, A. R., and McBride, T. J.: Antibiotics & Chemother. (Aug.) 1958. 3. Wennersten, J. R.: Antibiotic Med. & Clin. Therapy (Aug.) 1958. 4. Celmer, W. D., et al.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 476.

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lent deaths externally obvious or suspicious signs of violence are not present on the body. No consideration is given to the deaths of persons who have been unattended by a physician or who are found dead or dying when a physician arrives. Probably the majority of sudden and unexpected deaths occur under such circumstances.

Many deaths from natural causes occur unexpectedly. The word "natural" denotes death which results entirely from disease and in which traumatic injury or a poison has played no part. Natural death may occur in the presence of witnesses and without any obvious precipitating factor; or it may occur during physical exertion such as pushing an automobile, during sexual excitement, or during an altercation. A person may be found dead under circumstances more or less suspicious; the body may be found in bed. The possibility of foul play must be considered.

In a medicolegal investigation of the unexpected death of an apparently healthy person, the chief reason for an autopsy is to determine whether or not any form of violence has been the contributory factor. In many cases, even in the absence of external evidence of injury, an autopsy has shown that a person who apparently had died of natural causes actually was killed by violence. Furthermore, if the correct cause of unexpected death is established by autopsy, it may discourage unwarranted litigation for damages or insurance benefits. "Without autopsy there is too much room for speculation by misguided or interested medical experts."[2]

Sudden death is usually nontraumatic. Helpern has divided lesions which produce unexpected and sudden natural death into three categories:

1. The largest group is made up of natural disease processes of slow or insidious development which damage a vital organ without evoking any striking symptoms until there is a sudden cessation of function. The most common example is sudden death from coronary artery disease.

2. The second group comprises sudden and unexpected rupture of blood vessels accom-

(Continued on page A-42)

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Metamine®c
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Simplified, b.i.d. therapy for 24-hour defense against angina pectoris associated with emotional or nervous tension. Each sustained-release tablet contains 10 mg. METAMINE and ¾ gr. butabarbital.

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coughing for 6 to 8 hours with one "timed-release" tablet

Tussaminic is non-narcotic—the patient simply swallows one timed-release "double-dose" tablet before breakfast to work cough-free all day. Another tablet before dinner lets him relax cough-free all evening. A final tablet at bedtime lets him sleep cough-free all night. Thus, cough relief is measured in hours, not minutes.

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Each tablet contains:

TRIAMINIC® .....100 mg.
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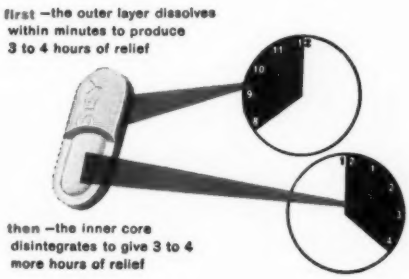
Dosage: 1 Tussaminic tablet before breakfast, dinner and at bedtime.

Tussaminic "timed-release" tablets provide prolonged cough relief. Each tablet contains two full doses of long-lasting antitussive, expectorant, anti-allergic and decongestant components.


first —the outer layer dissolves within minutes to produce 3 to 4 hours of relief
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panied by fatal hemorrhage, such as (a) the rupture of an aortic aneurysm, with hemorrhaging into the pericardial sac, (b) an aneurysm of the circle of Willis which produces subarachnoid hemorrhage, or (c) the rupture of an ectopic pregnancy, with bleeding into the peritoneal cavity.

3. The last category includes latent or overwhelming infectious diseases which develop without producing alarming or recognizable symptoms until death occurs; e.g., ambulatory lobar pneumonia or bacterial endocarditis.

An insurance company usually has the right to demand an autopsy in cases in which benefits for accidental death are claimed, but it does not have such right in cases in which benefits alone are involved. Life insurance policies have a provision known as the suicide clause. A commonly used stipulation is as follows: "If within two years following the date of issue of this policy and while it is in force, the insured, whether sane or insane, commits suicide, the company will be liable only for the amount of the premiums paid hereunder, which amount shall be paid in one sum to the beneficiary."

There have been instances during the two year suicide period in which an autopsy has been granted and even requested by the family in order to establish the true cause of death and thus allay any suspicion of suicide. Such a case occurred in Baltimore some years ago. The insured person was a busy physician in his middle 30s who had recently taken out a large amount of insurance. He had had no prior history of illness. One morning, shortly after he arose and 15 minutes after he had been heard talking on the telephone to a patient, his wife found him dead on his bed when she went to find out why he did not come to breakfast. A physician in the city certified the death without autopsy as having resulted from coronary artery disease. The suddenness of death as well as the fact that he had only recently been insured led to the suspicion that the deceased might have committed suicide. Although the insurer did not have the right to an autopsy, the family consented to have one performed about one month after death. The autopsy revealed that death was caused by a massive subarachnoid hemorrhage which resulted from the spontaneous rupture of a small aneurysm, no bigger than a match head, of one of the cerebral arteries at the base of the brain. Prior to its rupture, the aneurysm probably did not produce any symptoms and could not have been detected by the most searching physical examination.

Spontaneous subarachnoid or cerebral hemorrhage from the rupture of a small aneurysm of a cerebral artery is not an uncommon cause of unexpected death in adult persons. Such deaths occur under a variety of circumstances which often lead to suspicion of violence or suicide. Fatal subarachnoid hemorrhage may be erroneously attributed to trauma if the aneurysm ruptures as the result of an episode incident to violent physical exertion and if the aneurysm is so small it is not identified.

There are certain facts about coronary artery disease that should be remembered in relation to trauma. The distinction between a dormant condition and a progressive, although symptomless, disease is often overlooked and misapprehended by lawyers and the courts. The word "dormant" connotes something that is sleeping; e.g., a scar is a dormant process. Coronary artery disease may exist without recognizable symptoms, but it is not dormant because it is a progressive and irreversible disease. This disease can progress to an advanced state without evoking any symptoms. Unexpected death may be the first and last symptom of the disease.

Although any unusual stress may cause failure of a heart affected by atherosclerosis, heart-failure due to coronary artery disease usually occurs spontaneously and independently of any known physical stress. This type of heart-failure cannot be attributed to an episode of stress unless it occurs immediately thereafter. Moritz[3] has written, "If hours or days elapse between the stress designated and the subsequent attack of heart-failure, the relationship between the two is probably nothing more than just a fortuitous sequential coincidence."

An action was brought in the New York Supreme Court to recover under a policy of

(Continued on page A-44)

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efficacy?
long-lasting action?
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In low back pain, sprains and strains, PARAFLEX provides effective muscle relaxation on an *average dosage of only 6 tablets daily.* The benefits from a single dose of PARAFLEX persist for about *six hours.* Useful in a wide variety of traumatic, rheumatic, and arthritic disorders, PARAFLEX usually lessens spasm and pain *without* producing side reactions.

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insurance which provided a benefit if death resulted from bodily injuries sustained directly through accidental means and provided death did not occur as the result or by direct or indirect contribution of disease. The insured person was a salesman accustomed to carrying sample cases weighing up to 175 lb. for a block or two if he could not park his car near a store. On January 19, 1943, he fell on the floor in a sitting position. After the fall he continued to work regularly. He died on April 17, 1943, as the result of a coronary thrombosis. The beneficiary contended that the fall precipitated his heart attack. The autopsy showed that his heart was one and one-half times its normal size. The coronary vessels were sclerosed throughout. The lumen of the left coronary artery was so constricted at the opening that a probe the size of a pencil lead could not be inserted into it. The beneficiary contended that even though the coronary arteries were sclerosed, such condition was dormant and did not constitute disease. Proof of causal relation between the fall and death was given by a heart specialist. The court held that "In view of the positive direct testimony as to the actual facts disclosed by the autopsy, the opinion of the beneficiary's expert was of no probative value whatsoever, and a submission of the issue to the jury on that evidence would merely permit speculation and conjecture."[4]

Heart disease may cause injury. A person with advanced atherosclerotic heart disease is likely to die unexpectedly from heart-failure. If the person is standing or walking at the time of the heart attack he probably will fall. If he is driving an automobile he is likely to lose control of it and collide with some object. The resulting injury may be more or less severe. An autopsy is necessary to determine whether death resulted from heart disease or from the injury occasioned by heart disease.

Moritz[5] explained it this way: "If injury can be recognized to have occurred before death and if its effects can be recognized to be incompatible with life, *death can be said to have been caused by the injury*. If the heart disease found at autopsy constitutes an adequate explanation of death and if the injury either (1) occurred after death or (2) was of insufficient severity to have caused death independently of the heart disease, *death can be said to have been caused by heart disease*."

In a case[6] which was presented before the Court of Appeals of New York, a judgment was affirmed dismissing the complaint on the merits, since there was no proof that the insured's death was not caused directly or indirectly by heart disease. The evidence established that the insured had had progressive heart disease which was so serious that he had been receiving payments for total disability for 11 years. His physician testified to the seriousness of the heart disease and said that the patient's heart had become progressively weaker. The insured was driving his automobile along a smooth, dry Florida road when the car veered off the road and struck a pole. There were no skid marks or other marks on the road or over the course which the car traveled when it left the highway. The ignition was on and the shifting lever was in high gear. There was no evidence that the automobile was not in good operating condition before the accident. The insured sustained a crushed chest. The Dade County Physician expressed the opinion that death could have been caused either by the injuries resulting from the accident or by a heart attack just previous to the accident. The court held that on the proof "the jury could only speculate as to the cause of death or the contributory cause of death. Circumstances equally consistent with several hypotheses prove none."

Moritz[7] referred to the fortuitous coincidence of trauma and heart disease: "It is inevitable that the deaths of many of these persons will be preceded by some remembered incident of injury or stress. The ability of most persons to remember such events is tremendously enhanced by the prospect of double indemnity or workmen's compensation benefits if a cause-and-effect relationship between trauma and heart disease can be established. It should not be assumed that what follows an episode of stress was necessarily caused by that which preceded it. Unfortunately from the standpoint of justice, judges, lawyers and

(Continued on page A-46)

The Fishermen by Gerry Gersten

When they need more than fresh air to feel healthy... when their diet has gone completely wrong, what's probably needed first... and **most**... is the essential B-complex. That's a good time to

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juries are frequently unduly impressed by the sequence in which events have occurred."

Only a very few types of injuries cause sudden and unexpected death. Fracture of the neural arch in the atlas or axis usually means immediate death as a result of injury to the cord so near the vital medullary centers.

A woman gave an address to a taxicab driver and then sat back in the cab. When the address was reached she was dead, lying in a heap on the floor. A physician examined the body and determined that she had died from a coronary closure. It was ordered that her body be taken to the Office of the Chief Medical Examiner in New York.

The family asserted that they did not want an autopsy done. An attorney called the Chief Medical Examiner and threatened to bring an action against him for damages if he persisted. The Chief Medical Examiner told the attorney that he would have to take the risk of a lawsuit. The autopsy revealed a healthy heart. Further examination showed a snapped odontoid process and a crushed segment of the upper cord. Two years later an attorney called the Chief Medical Examiner and asked him if he would examine his files in the case and be prepared to testify in supreme court as to the cause of death. The Chief said, "Aren't you the attorney who threatened me with a lawsuit if I did an autopsy?" The reply was, "Don't rub it in, Doctor, please."

Epidural hemorrhage is rare except in association with a fracture, and the bleeding is not of a significant amount unless one of the meningeal arteries is torn or one of the venous sinuses is injured. Blood will collect quickly in case of arterial bleeding, and signs of increased intracranial pressure develop quite rapidly. Once clinical signs of increased pressure have appeared, sudden death is likely to occur from compression.

Sudden death also may occur as the result of attempting to swallow too large a bolus of food, with the result that the bolus enters the larynx instead of the esophagus. In some cases the bolus may be held in the pharynx and obstruct the laryngeal opening. When a foreign body starts to enter the larynx there is an immediate, violent effort to arrest and expel it by gagging and coughing. The cough is followed by a deep inspiration to gather more air for expulsion. The deep inspiration frequently causes the bolus to become tightly lodged in the larynx.[8,9]

The aspiration of vomitus into the air passages is a common cause of rapid death. Deep alcoholic stupor, ether anesthesia or coma predisposes to aspiration of vomitus.

Gonzales and associates[10] have pointed out that the cause of death may be overlooked unless the larynx and the trachea are examined. A middle-aged man was found dead in his jail cell. There were no unusual external signs. The autopsy revealed a severe grade of coronary arteriosclerosis and myocardial fibrosis sufficient to cause death under some circumstances. Dissection of the throat organs disclosed a rolled-up and crumpled necktie impacted in the pharynx; it apparently had been swallowed with suicidal intent. This obstruction was not visible through the mouth.

Comment

The cause of the unexpected death of a person in apparent good health can only be determined by a medicolegal autopsy which must also demonstrate whether or not death resulted from conditions which were not evident on casual examination.

REFERENCES

1. New York City Charter, Sections 1570 and 1571, as added by the New York Legislature in 1915.
2. Gonzales, T. A., Vance, M., Helpern, M. and Umberger, C. J.: Legal Medicine, Pathology and Toxicology. New York, Appleton-Century-Crofts, Inc., 1954, p. 102.
3. Moritz, A. R.: Trauma and heart disease. In Schroeder, O., Jr., editor: Physician in the Courtroom. Cleveland, Press of Western Reserve University, 1954, p. 88.
4. Kleinman vs. Metropolitan Life Insurance Company, 273 App. Div. 252, 76 N.Y.S. (2d) 618; see also Buchanan vs. Belsey, 65 App. Div. 58, 72 N.Y.S. 601.
5. *Ibid.*,[2] p. 97.
6. Ursaner vs. Metropolitan Life Insurance Company, 274 App. Div. 77, 79 N.Y.S. (2d) 760, aff'd 299 N.Y. 730, 87 N.E. (2d) 453.
7. *Ibid.*,[2] pp. 92, 93.
8. *Ibid.*,[2] pp. 480-482.
9. Moritz, A. R.: Pathology of Trauma. Ed. 2. Philadelphia, Lea & Febiger, 1954, p. 192.
10. *Ibid.*,[2] p. 104.

Radiology FOR PRACTICING PHYSICIANS

Gastric Ulcer

PAUL C. HODGES*

WHEN a competent radiologist reports the existence of a gastric carcinoma, the patient's family physician has the serious responsibility of getting him into the hands of a well-qualified surgeon as promptly as possible; when the radiologic report is gastric ulcer or is not definite between ulcer and neoplasm, the physician's responsibility is even greater. If he refers the patient to a surgeon, subtotal gastrectomy almost certainly will be done, regardless of the size or nature of the lesion; if he sends him to a gastroenterologist, the latter must be able to perform gastroscopy and exfoliative cytology; and if he attempts to follow the patient himself, he may live to regret it. I doubt that the general practitioner does either himself or his patient a service by undertaking to do his own gastrointestinal radiography, even as a preliminary screening process; but certainly he must know enough about the subject to be able to weigh the radiologic report intelligently as he considers it along with other factors in determining disposition of the case.

*Emeritus Professor and Chairman, Department of Radiology, University of Chicago, Chicago, Illinois.

Theoretically the x-ray differentiation between benign peptic ulcer and ulcerating gastric neoplasm is simple; however, in practice it frequently is difficult and sometimes is impossible. In theory the crater of a benign peptic ulcer is spherical or tongue-shaped; it protrudes beyond the serosa and shows little or no infiltration of the base and little or no interruption of the mucosal pattern except within the crater itself. Under antacid management, benign craters usually heal; if they recur, it frequently is at a new site. When gastric neoplasms ulcerate, the craters tend to have irregular shape, usually are withdrawn into the lumen of the stomach, and are located in intraluminal masses of tumor tissue. These tumor masses stiffen the gastric wall about the crater and interrupt the mucosal pattern for a variable distance beyond the crater. Of course, hyperacidity is unusual in gastric neoplasm, but when it is present and when antacid therapy is followed by healing of a crater, the recurrence usually is at the original site. However, inflammatory reaction about a benign crater may produce an x-ray appearance un-

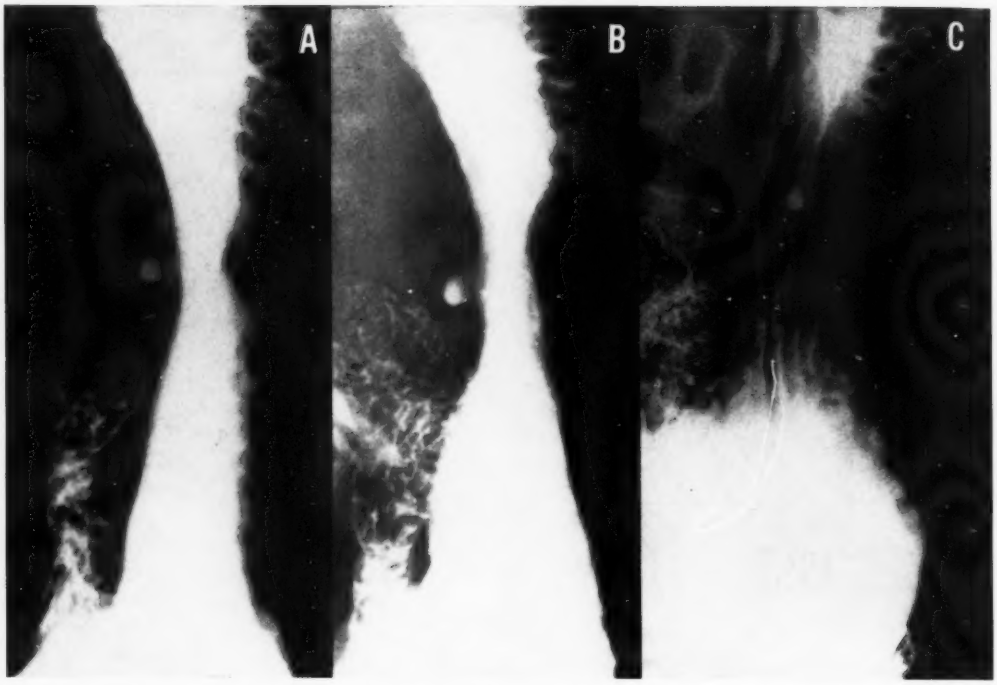

FIGURE 1. Small benign gastric ulcer measuring 5 by 10 mm. The craters of gastric ulcers frequently are small and most commonly lie along the lesser curvature of the body of the stomach. A and B. The patient has been rotated to bring the ulcer into profile. C. Ulcer seen *en face*. The radiologist called the lesion benign, but the surgeon, fearing malignancy, did a partial gastrectomy. Histologically, the lesion was benign.

distinguishable from neoplastic infiltration, and very small neoplasms may ulcerate so promptly and so completely as to leave only microscopic residua of tumor.

Small Solitary Craters

When an ulcer is small and solitary, protrudes beyond the serosa, and has normal-appearing mucosa about it, the x-ray diagnosis is benign ulcer, and this usually proves to be correct (figure 1).

Hourglass Deformity

In the early days of gastric radiology, fluoroscopy and radiography had such limited scope that only gross lesions could be detected. One of the most dramatic findings was a deep incisura on the greater curvature opposite a lesser curvature crater. Because the incisura divided the stomach into upper and lower portions, it was termed hourglass deformity (figure 2). Possibly the condition used to be more common when acute ulcers were apt to go undiagnosed and untreated until symptoms of obstruction brought them to light. Certainly the finding is a rarity today.

Healing as an Indication of Benignancy

The ulcer crater that heals promptly under antacid therapy usually, but not invariably, is benign. At the first examination of the case illustrated in figure 3, the crater on the lesser curvature of the body of the stomach measured 3.5 cm. in diameter and 1.5 cm. in depth, and there was more than a little reason to fear neoplastic infiltration of the gastric wall about it. However, the patient was given a trial of antacid therapy, and within one month the crater was greatly reduced in size and mucosal folds passed directly into it, indicating that the infiltration had been inflammatory rather than neoplastic. Five months after the first examination, healing was complete, leaving

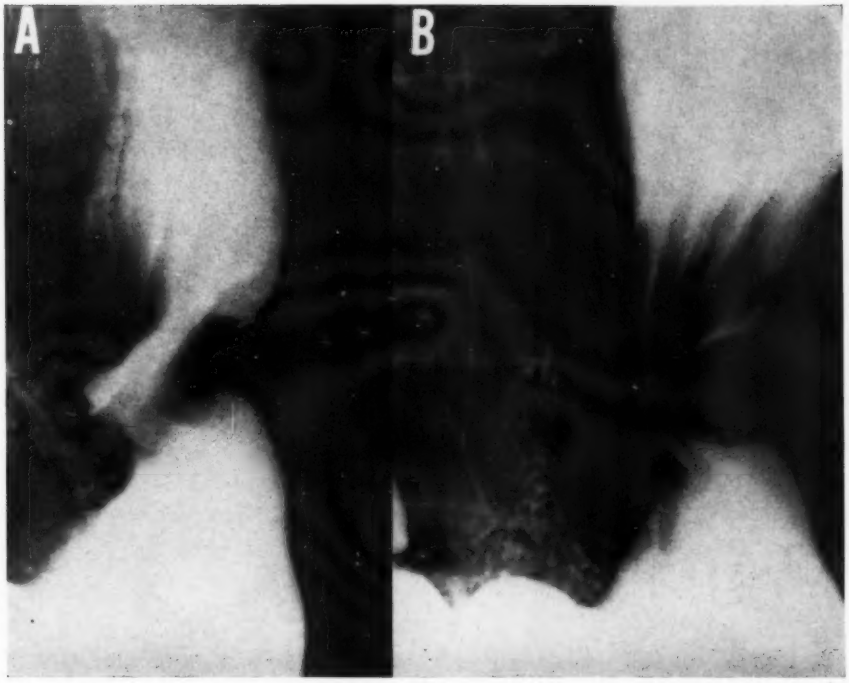

FIGURE 2. Gastric ulcer producing hourglass deformity. A. Ulcer crater measuring 3 by 6 mm. at lesser curvature of the body of the stomach in a woman with a one year history of melena and cramping abdominal pain. A deep incisura of the greater curvature at the level of the crater divides the stomach into upper and lower portions, the so-called hourglass deformity. B. Four months after institution of medical treatment; the crater has healed but deformity persists.

merely a puckered scar at the lesser curvature.

Healing as a Misleading Factor in Malignancy

While surgeons and internists continue to disagree as to whether benign gastric ulcers ever undergo malignant degeneration, it is recognized by all that small neoplasms may ulcerate so promptly and so completely as to produce a radiographic appearance identical with benign gastric ulcer. Furthermore, a patient with a benign gastric ulcer may have a small neoplasm as well, and there seems to be statistical proof that gastric neoplasm is prone to develop in patients who have chronic gastric ulcers.

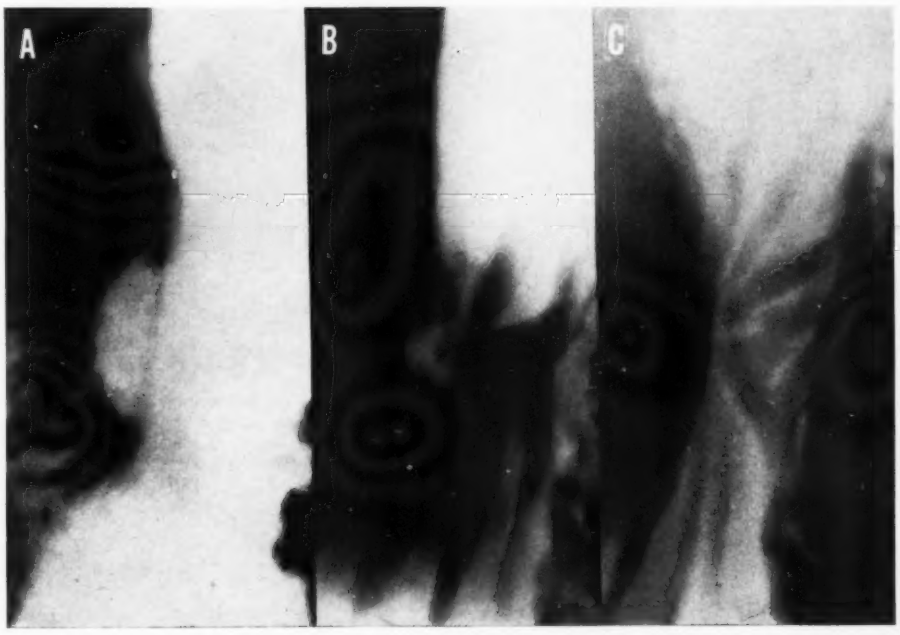

FIGURE 3. Healing benign peptic ulcer. A. Located on the lesser curvature of the body of the stomach, the ulcer crater measures 1.5 by 3.5 cm. B. One month after irradiation and antacid therapy; the crater is much smaller. C. Five months after the first examination; the crater has healed, but there is persistence of mucosal scar, with mucosal folds radiating from the former ulcer site.

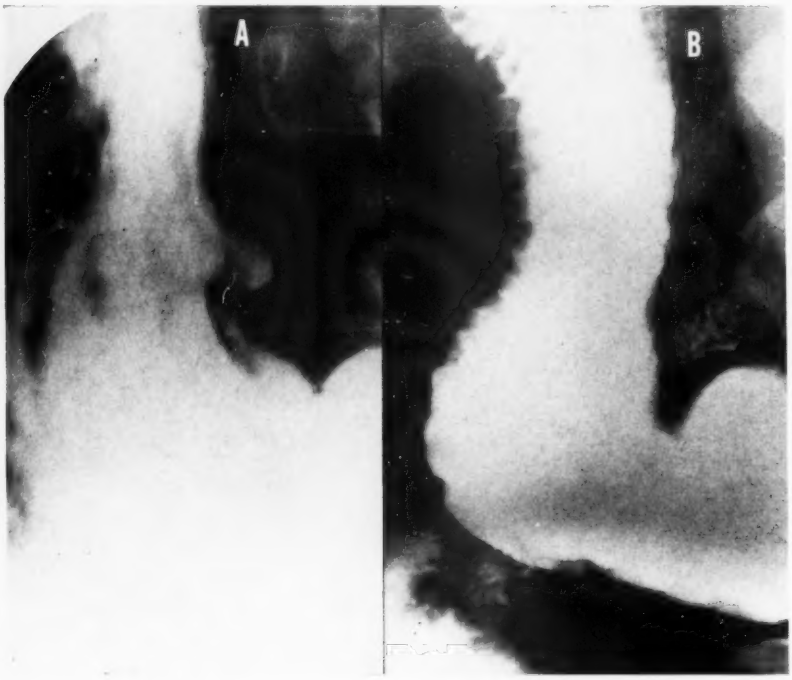

FIGURE 4. Malignancy in a healed peptic ulcer. A. Ulcer crater measuring 1.5 by 1.5 cm. protruding beyond the margin of the serosa at the lesser curvature of the body of the stomach. B. Two months later; crater has healed but subtotal gastrectomy showed neoplasm.

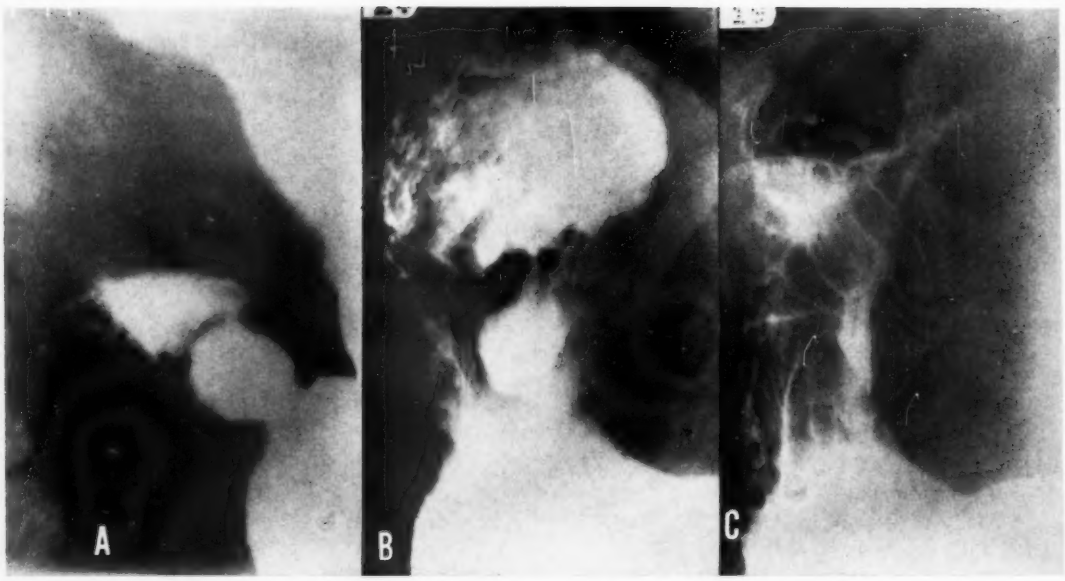

FIGURE 5. Neoplasm developing in old ulcer site. A. This 1 cm. benign-appearing crater at the lesser curvature of the body of the stomach healed under management. B. Seven years later; a huge 2.5 by 3.5 cm. malignant-looking crater lies retracted into the lumen of the stomach at the old ulcer site. C. One month following the x-ray in figure 5B and after irradiation of fundus; the crater has healed, leaving a puckered scar. Subtotal resection one month later showed neoplasm.

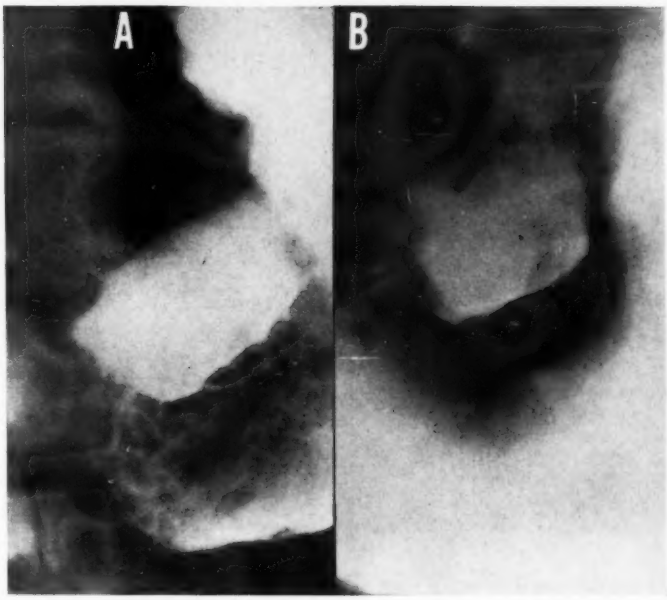

FIGURE 6. Huge benign peptic ulcer measuring 8 cm. in diameter. We interpreted the halo at its base as neoplasm. Subtotal resection showed it to be benign.

In the case illustrated in figure 4, a large benign-appearing crater protruded from the lesser curvature of the stomach, just proximal to the incisura angularis. Two months later it had healed completely, but, meanwhile, exfoliative cytology had become positive; therefore, a few days following the making of the x-ray shown in figure 4B, a subtotal gastrectomy was done. The pathologist reported superficial carcinoma in the region of a chronic gastric ulcer.

Neoplasm Developing in Old Ulcer Site

Figure 5 shows a shallow, 1 cm. ulcer crater which developed in a 47 year old man at the lesser curvature side of the body of the stomach; it healed under management. Seven years later a 2.5 by 3.5 cm. ulcer crater was found at almost exactly the same site on the lesser curvature of the body, and there seemed to be neoplastic infiltration of the wall about it. However, the referring physician, believing the lesion to be benign, put the patient on antacid therapy and irradiation of the gastric fundus. One month later the crater had healed, but with persistence of a puckered scar; in the meantime the exfoliative cytology had become positive. At the time of subtotal resection a few days later, the surgeon believed he was dealing with a benign ulcer, and only at mi-

FIGURE 7. A benign gastric ulcer measuring 1.5 by 3 cm. at lesser curvature of body of stomach in a 50 year old man. Although the lesion appeared to be malignant, subtotal gastrectomy revealed it to be benign.

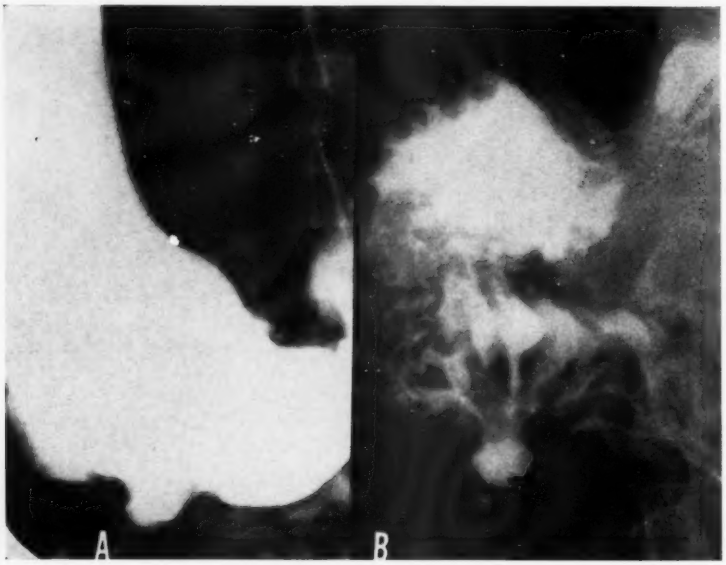

FIGURE 8. Benign crater measuring 1.5 by 2 cm. protruding from greater curvature of stomach. A. Filled view. B. Compression view, showing mucosal folds extending without obstruction into the crater. One week later, subtotal resection showed the ulcer to be benign. Two weeks later a new crater had developed in the gastric stump; two and one-half years after the first operation there were two more craters. These were excised and the gastroenterostomy was taken down. Following a vagotomy, there was no further recurrence.

croscopy was the malignant nature of the lesion established.

Because Ulcer Crater Is Large Does Not Prove It Is Malignant

While it is true that most benign ulcer craters are relatively small and that most of the large craters we see represent ulceration in neoplasm, largeness alone does not justify a diagnosis of malignancy. In the case of the 65 year old man illustrated in figure 6, there had been symptoms for three months. An enormous 8 cm. ulcer crater was found at the lesser curvature side of the stomach at the incisura angularis; in fact, it was so large that it was difficult to get it onto our small films. We assumed that the condition was ulcerating neoplasm, and at operation five days later subtotal resection was done; however, microscopic examination showed that the lesion was benign.

Failure of Ulcer Crater to Protrude Beyond Normal Margin of Stomach Does Not Absolutely Establish Malignancy

In the case illustrated in figure 7, the large, 1.5 by 3 cm. ulcer crater at the lesser curvature of the body of the stomach fulfills practically all of the x-ray criteria for malignancy. It is withdrawn into the body of the stomach rather than protruding beyond it; the surrounding gastric wall is stiff; and the mucosal folds do not extend into the crater. The radiologist diagnosed it as malignant, and, at the time of operation, the surgeon's preoperative and postoperative diagnoses were neoplasm. Only when the tissue was examined was the benign nature of the lesion established.

Location on Greater Curvature Not a Dependable Criterion of Malignancy

It is true that most benign gastric ulcers occur on the lesser curvature of the stomach and that it is not particularly uncommon to find ulcerating neoplasms on the greater curvature, but only by false logic does this lead to the conclusion that by virtue of these facts any ulcer crater encountered on the greater curvature is malignant.

In the case illustrated in figure 8, a 1.5 by 2 cm. ulcer crater projected straight downward from the horizontal portion of the greater curvature of the body of the stomach, with mucosal folds projecting directly into it and without any evidence whatever of a collar of neoplasm or even inflammatory tissue about the neck.

One of our junior radiologists incorrectly diagnosed the lesion as malignant, presumably because of its greater curvature location; perhaps for this reason, at the time of operation a week later, the preoperative diagnosis was malignant gastric ulcer. A subtotal gastrectomy was done and at gross and microscopic examination of the tissue no neoplasm was present.

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Through the Stethoscope

With this issue, POSTGRADUATE MEDICINE is pleased to offer the first of a new monthly feature to appear under the heading "Through the Stethoscope." Alternating as authors will be Dr. Noah D. Fabricant and Dr. Wendell J. S. Krieg, with the former inaugurating the department. The material to be included may perhaps best be characterized as subclinical but definitely medical. Although it is intended primarily for diversion, the Editors hope that it will lead to some contemplation of a philosophical nature on the part of the reader.

The Authors

DR. Fabricant graduated from the University of Illinois College of Medicine and is currently associated with that school as clinical assistant professor of otolaryngology. A diplomate of the American Board of Otolaryngology, Dr. Fabricant is a recipient of the Casselberry Prize Award of the American Laryngological Association for meritorious research on upper respiratory tract infections and nasal medication. He is an associate editor of the *Eye, Ear, Nose and Throat Monthly* and a contributing editor of the *American Journal of the Medical Sciences*. He has written extensively for both medical and lay publications and is the author or editor of 11 books, including "The Common Cold," "Headaches," "Nasal Medication," "Modern Medication of the Ear, Nose and Throat," "Why We Became Doctors," and "A Treasury of Doctor Stories."

Among his memberships in professional organizations, Dr. Fabricant includes the American Academy of Ophthalmology and Otolaryngology, American Rhinological, Laryngological and Otological Society, Sigma Xi, American Association for the Advancement of Science, Society of Midland Authors, Society of Medical History of Chicago, and the American Medical Writers' Association.

DR. Krieg came to Northwestern University Medical School in 1944. Before that he was a member of the faculty of New York University. He started there as an instructor in anatomy in 1929 and was appointed assistant professor in anatomy in 1938. His first appointment at Northwestern was associate professor of neurology in the Institute of Neurology. In 1946 he became professor of neurology and director of the Institute, and since 1948 has been professor of anatomy.

Dr. Krieg, who was born in Lincoln, Nebraska, in 1906, received his B.S. degree in medicine from the University of Nebraska and his M.S. and Ph.D. degrees, both in anatomy, from New York University. An accomplished artist as well

(Continued on page A-72)

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welcome relief of spasm and pain is continuously reported in functional G-I disorders, such as irritable, spastic colon syndrome; peptic ulcer; biliary dyskinesia; pylorospasm; and infant colic.

sure

relief can be expected . . . even in patients where other antispasmodics have failed.[1-3]

direct

dual antispasmodic action is specific to the G-I tract. Spasm pain is relieved by direct relaxation of the smooth muscle and postganglionic parasympathetic nerve blockage.

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1. Chamberlain, D. T.: Gastroenterology *17*:224, 1951. 2. Hock, C. W.: J.M.A., Ga. *49*:124, 1951. 3. Derome, L.: Canad. M.A.J. *69*:532, 1953. 4. Cholst, M., Goodstein, S., Berens, C., and Cinotti, A.: J.A.M.A. *166*:1276, 1958.

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as author, Dr. Krieg has had numerous publications in the field of anatomy and neuroanatomy and has also created most of the illustrations in five books he has written. In addition to membership in professional organizations, he has been active with the Chicago Literary Society and the Caxton Club, a leading Chicago writers' group.

Dr. Krieg is a member of the American Association of Anatomists; Corporation, Marine Biological Laboratory, Woods Hole, Massachusetts; a founding member of the Cajal Society; Chicago Neurological Society, the American Neurological Association and the American Academy of Neurology.

Practitioners of Bed Rest

NOAH D. FABRICANT

MANY of us are convinced that getting our patients out of bed early and having them walk about frequently, if not energetically, prepares them for recovery. "Get up," our patients are urged, "and move about. That is the way to restore good health."

Such medical admonishment, admirable though it may be, has not always fallen on receptive ears. Take the cases of four famous men and women whose achievements have been admired universally. Charles Darwin, Florence Nightingale, Elizabeth Barrett Browning and Marcel Proust literally led a life of rest. They detested exercise, they despised fresh air, and they lay about in bed, sometimes for years. Indeed, they never engaged in something called a little rest. If a little was good, a lot was certain to be much better.

Charles Darwin, whose "Origin of Species" at the time it was published revolutionized the world of science, actually never went to bed to improve his health. He merely spent a great deal of his life reclining on a sofa. From the time he was 22 years old Darwin was convinced he had heart disease. He was certain he would be rejected on grounds of poor health when he applied for the post of naturalist on the Beagle, the hardy little vessel that was to make an epochal five year voyage down the coast of South America. To his surprise he was accepted to lead a life of activity.

On one occasion, during a disastrous trip into the interior, Darwin's stamina permitted him to struggle on to find water when most of the other men in the party of exploration were too exhausted to move. Nonetheless, he continued to have fatigue, sinking feelings, dizziness, insomnia and headaches. In his old age, he was to find it too tiring to look out of a window. Darwin's schedule called for two hours of writing or experimentation. He had breakfast at 7:45 A.M. and then worked until 9:30 A.M. After this he lay down on the sofa for a couple of hours, then worked only until noon. If what he did had gone well, he would say in a highly contented voice, "I've done a good day's work."

Florence Nightingale, on the other hand, stayed in bed, except for brief intervals, for more than half a century. Like Darwin, she also believed she had heart disease. Despite the fact that she was convinced her life hung by a thread, she saw a stream of cabinet ministers, viceroys and politicians and influenced their political decisions, all from the vantage point of a bed. Unduly concerned with her health, Florence Nightingale signed many wills and distributed her possessions not once, but many times. She died in 1910 at the age of 90 years.

Elizabeth Barrett Browning, who wrote some of the finest poetry any woman has ever written in the English language, spent three-quarters of her life in bed. She believed she had a disease of the spine, although her doctors were never able to find anything wrong. Her bedroom was unbearably stuffy, and from October to May the edges of the windows were sealed with brown paper to exclude the faintest trace of fresh air. Yet one day she rose from her bed to elope with Robert Browning and to live a happily married life in Italy and have a healthy son.

Marcel Proust, author of "Remembrance of Things Past," one of the greatest novels of the twentieth century, had asthma and spent

(Continued on page A-74)

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most of the final 10 years of his life in an unventilated bedroom. The room was always thick with the smoke of fumigation; medicine bottles and empty jars were everywhere, mixed with masses of manuscript. Proust remained in bed for longer and longer periods, writing, studying, receiving his friends, and going out only on rare occasions, and then only at night. When he was 51 years old he contracted pneumonia. His last hours were devoted to proofreading.

ENDURANCE TEST

When he harps on his favorite ailment,
Which is likewise your own complaint,
And you listen without curtailment—
Brother, that's self-restraint!
Stephen Schlitzer

Sherlock Holmes as Diagnostician

Sherlock Holmes, the most delightful of fictional detectives, is perhaps the most widely known character in modern literature. The entire Holmes saga, consisting of 60 durable adventures, bears testimony to the supremacy of astute observation, skill in eliciting facts, and deductive reasoning—ingredients as necessary to the successful tracking down of disease as they are to solving crime. Medical diagnosis today is deduced from premises elicited by inspection, examination, attention to spoken details, and data provided by laboratory tests and precision instruments.

Arthur Conan Doyle, as nearly everyone knows, was the creator of Sherlock Holmes. Had not the printed word conferred on him universal renown, overshadowing the fact that originally he was a member of the medical profession, Doyle's name would have been forgotten long ago. When he had been in practice for some time, Doyle received a letter from the government informing him that his income tax report for the previous year had been found "most unsatisfactory." The harassed Doyle, who earned but £154 (less than $750) his first year as a doctor and never more than £300 after eight years of general practice, scrawled two words across the official letter and mailed it back. The letters were: "I agree."

The original model for Sherlock Holmes was Dr. Joseph Bell, a skilled surgeon, a popular teacher at Edinburgh, and a prolific writer. As a medical student, Doyle was deeply impressed by Bell's diagnostic intuitions, keen observations and startling deductive powers. Bell emphasized the importance of observation, telling the medical students: "Try to learn the features of a disease or injury as precisely as you know the features, the gait, the tricks of manner of your most intimate friend. Him, even in a crowd, you can recognize at once. It may be a crowd of men dressed alike, and each having his full complement of eyes, nose, hair and limbs. In every essential they resemble one another; only in trifles do they differ and yet, by knowing these trifles well, you make your recognition or your diagnosis with ease." The rules of Sherlock Holmes echoed Bell's real-life gospel.

Bell's influence on Doyle is apparent throughout the Holmes saga, although there are suggestions that the invention of the immortal detective conformed to a fundamental logic in Doyle's own temperament. Inflections of Holmes' thinking are evident in a number of pithy declarations: "You have not observed, and yet you have seen." "It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts." "Never trust to general impressions, but concentrate yourself on details." "When you have eliminated all which is impossible, then whatever remains, however improbable, must be the truth."

MIRACLE DRUGS

The chemist makes them,
The druggist counts them,
The patient takes them—
I can't pronounce them.
Stephen Schlitzer

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(as reported in *Time*)

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In the presence of trichomoniasis, many physicians now routinely specify prophylactics to prevent husband-wife re-infection. ". . . Trichomonas vaginalis in the male is the principal factor of re-infection in the female. . . ."[1] Husbands will cooperate more readily in the treatment plan for wives if you specify RAMSES, the prophylactic with "built-in" sensitivity.

1. Feo, L. G., et al.: J. Urol. 75:711 (April) 1956.

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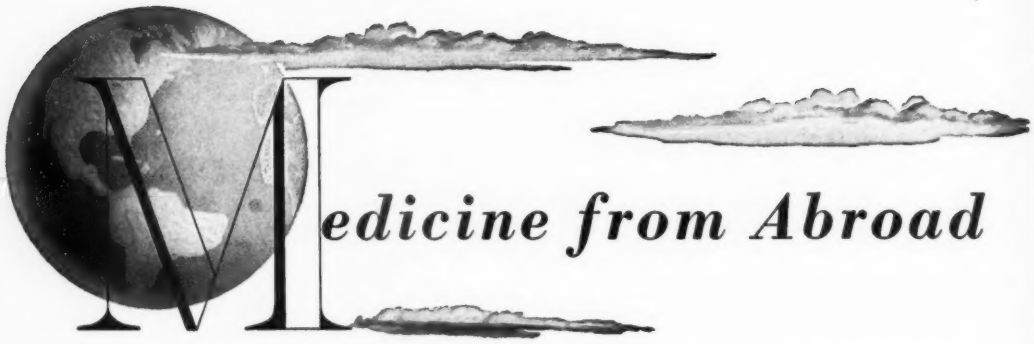

Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AUSTRALIA

Use of fluoroscopes in shoe stores—In a survey of shoe-fitting x-ray fluoroscopes in New South Wales, Alan Bell, director, and H. M. Whaite, senior scientific officer, Division of Industrial Hygiene, Department of Public Health, found that the present usage of these machines is unsatisfactory in regard both to radiation exposure to the customer and the salesman and to existing operating practices (M. J. Australia 1:729 [May 31] 1958).

There is little likelihood that the machines will cause somatic damage. However, from the genetic point of view, it is undesirable to expose persons to unnecessary radiation. The survey showed that some salesmen could receive during their working lives, in fact, one had received, a gonadal dose greater than that recommended.

Authorities in various countries have stated that such machines should not be used in shoe stores. A few opinions are quoted. D. J. Stevens, director of the Commonwealth X-ray and Radium Laboratory, Melbourne, said at the forty-fourth session of the Industrial Hygiene Committee of the National Health and Medical Research Council of Australia that "it is important that persons should reserve their ration of radiation and not dispose of it on nonessentials such as footwear fluoroscopes."

"There seems little if any excuse for x-ray examination of the feet of customers in shoe shops . . . it adds unnecessarily . . . to the difficulty of keeping within the maximum permissible dose. . . . It should be abolished" (M. J. Australia [March 30] 1957).

E. P. George, director of medicophysics, St. Vincent's Hospital, Sydney, stated that "I'd gladly see them abolished . . . of all x-ray appliances the pedoscope is by far the most dangerous . . . the machine is a useless and dangerous sales gimmick" (*Daily Telegraph* [May 13] 1957).

"The practice of routinely examining the feet by x-rays when fitted with shoes is of dubious value . . . it is in our view hardly justifiable. We hope that the procedure will be abandoned, except when prescribed for orthopedic purposes" (Medical Research Council, 1956).

Treatment of pruritus ani—In a recent article in the *Medical Journal of Australia,* Dr. Edward Wilson pointed out that pruritus ani may seem unimportant to the unafflicted person, but in truth it is not a triviality; it is a peculiar problem which requires careful handling. Avoiding scratching and keeping the anus and perianal skin dry comprise the basic treatment in common cases with no apparent cause. (Similarly, keeping the abdominal skin clean and dry will relieve itchiness around a colonic stoma.)

Before prescribing treatment, a careful general and local examination is carried out; unless the condition is quickly relieved by keeping the anus and perianal region clean and dry, the feces, the urine and the scrapings from the perianal skin should be examined. Special tests, such as

(Continued on page A-89)

an attempt to cultivate the scrapings on Sabouraud's agar, only occasionally will be required.

Repeated application of any ointment with a greasy or water-soluble base to the perianal skin and anus is usually followed by local changes. Accordingly, it is best to avoid such preparations, except for short periods. This restriction applies with added emphasis to ointments containing local anesthetic agents, which are irritating to the skin even when used alone.

The most firmly established agent in the treatment of pruritus ani is hydrocortisone ointment, and the different concentrations from 1 to 5 per cent appear to be equally effective. The rapid relief provided by these ointments is sometimes gratifying, even in tormenting cases, but it is not sustained. In some cases they do not provide even temporary relief.

In Wilson's experience the only antibiotic ointment that has been of any appreciable value in treating pruritus ani is neomycin. This has been used occasionally for treating resistant bacterial infections of the skin secondary to the scratching, but its effect has been only evanescent.

Instead of the ointments, antimycotic agents may be used. Those most often applied to the perianal region are Castellani's carbolfuchsin paint and aqueous and alcoholic solutions of gentian violet. These dyes are applied with a brush. They should not be used for more than 10 or 12 days, since they may cause chemical dermatitis. Whitfield's ointment (50 per cent with or without 0.5 to 1 per cent thymol) is used only after these dyes have failed to give relief.

Excessive perspiration is the chief indication for grenz ray or x-ray therapy in pruritus ani; but this treatment should not be repeated, for it may produce irradiation dermatitis, with the skin dry, thin, itchy and easily damaged by scratching. Instead of using irradiation, sweating may be reduced by applying a lotion such as 5 per cent aqueous solution of aluminum acetate. The proprietary preparations used to control underarm perspiration are too strong to use on the perianal skin.

After a thorough consideration of all possible causes, if no explanation is found for the pruritus ani except dampness and the resulting pruritic changes in the perianal skin, Wilson advised the following treatment. The perianal skin is kept dry, and scratching is avoided. After defecation the area is washed with cotton wool and the soap is completely removed from the skin. After the area has been dried with more cotton wool, a powder consisting of equal parts of zinc oxide, starch and boric acid is applied with cotton wool or a powder puff. If there is a history of fungous infection, 1 per cent salicylic acid is added to the powder for a few days.

Underclothes and pajamas should be loose-fitting, made of open-weave cotton, and with short sleeves and legs. Wearing nylon is definitely contraindicated, and an excess of clothes or bedclothes should be avoided. If symptoms become worse when the patient is in bed, the perianal area should be washed with cold water and dried immediately prior to retiring.

Most patients with severe pruritus ani would probably agree to operation if it were suggested to them; however, with the exception of those operations directed at concomitant lesions of the anus and the anal canal, operative treatment of pruritus ani has been superseded by medical measures.

Pathologic findings in deaths during influenza epidemics—In postmortem examinations conducted during an influenza epidemic, K. M. Bowden and E. L. French observed the following histologic features: (1) varying degrees of epithelial degeneration of the tracheobronchial tree; (2) marked hyperemia of the tunica propria; (3) infiltration of the tunica propria and sometimes of the epithelium by inflammatory cells, among which plasma cells are often conspicuous; (4) varying degrees of degeneration of the epithelium of the muciparous and serous glands; (5) plasma cells possibly predominating about these damaged glands; (6) toxic myocarditis.

It was suggested that the association of plasma cells with the muciparous and serous glands of the trachea and bronchi may be related to local antibody production.

AUSTRIA

Diagnostic value of test for adenosine deaminase activity in blood plasma—At a recent meeting of the Society of Physicians in Vienna, Drs. F. Seelich and K. Letnansky reported their findings in determining the values of adenosine deaminase activity in the blood plasma of 350 persons, some who were sick and some who were healthy. They found unequivocally increased positive values in 92 per cent of patients with pulmonary cancer and in 78 per

(Continued on page A-90)

cent of patients with tumors, and abnormally high values in patients with chronic myeloid and lymphoid leukosis. Positive values also were recorded in 62 per cent of tuberculous patients. On the basis of these findings, they concluded that higher values of enzyme activity may occur in patients with cancer or inflammatory disease.

In spite of such observations, the diagnostic value of the test is still debatable. The question was asked whether the degree and the extent of the carcinoma located in the bronchi influenced results of the test. Seelich stated that according to available data the test is still unsuitable for diagnosing early bronchial cancer. However, the values of the test and the severity and extent of the disease seem to be directly related.

Treatment of poisoning caused by irritating gases—In a report to the Society of Physicians, Dr. V. Lachnit described the possibilities of occupational intoxication by nitrous fumes, the gas causing the most significant irritation from the viewpoint of industrial medicine. The prognosis of poisoning caused by irritating gases appears to be unfavorable because of the development of primary edema of the lungs and so-called chemical pneumonia, which results in carnifying pneumonia or obliterating inflammation of the smallest bronchioles, or both.

Lachnit reported a case of accidental rather than occupational poisoning in a 35 year old electrician employed at an industrial plant. His job was to clean up the spillings of fuming nitric acid. After a typical period of latency, pulmonary edema developed, in spite of the immediate initiation of cardiotonic therapy with oxygen and calcium and the additional administration of antibiotics. After concentrated treatment with prednisolone, the clinical as well as the roentgenologic signs in the lungs promptly regressed. The patient continued to take small doses of prednisolone after he returned home, but when a hivelike rash appeared the medication was stopped by order of a dermatologist. Four days later, the patient had a high fever, became short of breath, and had a constant urge to cough.

A roentgenogram taken at this time showed numerous newly developed, very small and partly striated densities which seemed to be considerably denser than the original infiltrations. Return to prednisolone therapy, initially combined with antibiotics and drugs to aid circulation, produced almost complete clearance of the lung fields, restored plasma protein values to normal levels, and decreased the number of white blood cells after a rather long-lasting leukocytosis. The treatment was continued for some time.

Lachnit emphasized that in cases of poisoning caused by irritating gases, cortisonelike substances should be given in the early stages both to combat the initial inflammatory edema of the lung and to treat the chemical pneumonia. Moreover, this treatment must be continued long enough to prevent such serious chronic complications as carnifying bronchopneumonia or obliterating inflammation of the smallest bronchioles, or both.

BRAZIL

Treatment of South American blastomycosis—A new antibiotic, amphotericin B (Fungizone), has proved to be remarkably effective in treating South American blastomycosis, an infection caused by *Blastomyces brasiliensis*. This disease was originally considered a mycotic skin infection, since the lesions seemed to be localized in the mucous membrane and in the skin. Further studies proved it also affects the internal organs. It is believed that this fungus is found on vegetables and that it usually penetrates the organism through the mucous membrane of the oropharynx. The parasite can also enter the body through the rectum. South American blastomycosis occurs most frequently in rural areas; however, cases have been found in urban locations.

In 1940, Oliveiro Ribeiro investigated the efficiency of the sulfonamides in treating the fungus. Recently, the antifungus amphotericin B was developed from *Streptomyces* isolated from samples of earth taken from the banks of the Orinoco river.

Brazilian researchers have obtained excellent results in treating the cutaneous-mucous types of South American blastomycosis with amphotericin B. Side effects occurring when the remedy is given intravenously have been reduced by the simultaneous administration of cortisone or similar remedies.

Total gastrectomy—In the opinion of Professor Fernando Paulino and Drs. Paulo Pernambuco and Domingos E. Junqueira de Moraes, total gastrectomy should not be performed to remove tumors of the pyloric region, but should be restricted to tumors of the body or the cardiac region of the stomach and diffuse neoplasms. Total gastrectomy did not prove to be an effec-

(Continued on page A-92)

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Dosage: The recommended adult dose is 1 Gm. (2 tablets) the first day, followed by 0.5 Gm. (1 tablet) every day thereafter, or 1 Gm. every other day for mild to moderate infections. In severe infections where prompt, high blood levels are indicated, the initial dose should be 2 Gm. followed by 0.5 Gm. every 24 hours.

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Syrup: Each teaspoonful (5 cc.) of caramel-flavored syrup contains 250 mg. of sulfamethoxypyridazine. Bottle of 4 fl. oz.

references:
1. Grieble, H.G., and Jackson, G.G.: Prolonged Treatment of Urinary-Tract Infections with Sulfamethoxypyridazine. *New England J. Med.* 258:1-7, 1958.
2. Editorial: *New England J. Med.* 258:48-49, 1958.

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*Reg. U. S. Pat. Off.

tive palliative treatment either for tumors with distant lymphatic metastases or for those which had spread extensively to neighboring organs.

Inguinal hernia in infancy—In the magazine of the Brazilian Medical Association, Professor Virgilio Carvalho Pinto reported on the treatment of inguinal hernia in 2000 children whose ages were from six hours to 15 years. Considering the physical and psychologic disturbances caused by the hernia, the complications that may occur, and the benignity of surgical treatment, Pinto suggested that early operative correction is indicated. In his experience, the technic of high ligature of the hernial sac on a prefunicular plane produced excellent functional results, with no recurrent or postoperative complications.

Hydrocortisone in dermatology—Dr. Norgerto Bellitoni recently reported on the topical use of hydrocortisone in treating infantile and atopic eczema, infectious eczematoid dermatitis, eczema nummulare, contact dermatitis, psoriasis and sycosis staphylogenes. The medication completely cured the skin condition in 10 of 24 patients; the remaining patients, including two with psoriasis, showed marked improvement. From an analysis of the literature and from his own clinical observations, Bellitoni has drawn the following conclusions: (1) Topical application of hydrocortisone provides an effective therapeutic measure in the treatment of skin diseases of an eczematous type. (2) The preferred concentration of hydrocortisone is 2.5 per cent. (3) Favorable results are obtained quickly and can be maintained through the continued use of the ointment. When relapses occur, they tend to be milder than the original condition. (4) The conditions which respond most favorably to local application of hydrocortisone are atopic dermatitis, including infantile eczema; contact dermatitis; pruritus ani and vulvae; seborrheic dermatitis, and eczema nummulare. (5) The rare instances of sensitivity are usually caused by the ointment base. (6) Fluorocortisone acetate (9-α-fluorohydrocortisone) should not be applied indiscriminately. Its use requires special clinical precautions because of the higher rate of absorption through the skin or mucous membrane lesions. (7) A combination of an antibiotic and hydrocortisone is valuable, but the antibiotic used should be a type not commonly employed systemically. Neomycin is the preferred topical antibiotic.

Kinesis—Professor Jacque Houli in *Resenha clínico-científica* has suggested the need of considering the articular-ligamentary apparatus as an anatomic-physiologic unit. Similar to the nephron, the unit of excretion, and to the neuron, the structural unit of the nervous system, the locomotor apparatus also has its own anatomic-physiologic unit, Cinesion (*sic*), comprised of the joints (bone, epiphysis, cartilage, fibrocartilaginous apparatus, synovial membrane and fluid, articular cavity, capsule and ligaments), the blood and lymphatic vessels and circulation. "Cinesion" also includes the skin that covers the joints, the voluntary and involuntary muscles responsible for motion, the sensory and motor nerves of muscles and skin, and the sympathetic nerves. Since its component parts have a common origin and a simultaneous development, "Cinesion" may be considered in a unitary way as the basic organ of the locomotor apparatus.

DENMARK

Errors in diagnosing cerebral apoplexy—In a recent issue of *Ugeskrift for laeger*, Dr. Jørgen Marquardsen reported that of 291 patients in whom a diagnosis of cerebral apoplexy had been made on clinical findings, autopsy revealed an intracranial tumor in six and a chronic subdural hematoma in six. The errors in diagnosis were due to several factors: the patients' advanced age, acute onset of cerebral symptoms, absence of signs of intracranial hypertension, temporary remission of the condition, evidence of cardiovascular disease, and, in patients with subdural hematoma, a history of apparently insignificant traumatic episodes. Although a correct antemortem diagnosis probably could have prevented death in several patients with subdural hematoma, most frequently the undiagnosed tumors were inoperable malignant gliomas.

A correct diagnosis in cerebrovascular accidents can be obtained only by cerebral angiography. When facilities for this procedure are not available, diagnostic errors can be reduced by focusing attention on the course of the disease and the manner in which the signs and symptoms develop. An expanding lesion should be suspected in the following instances: (1) insidious onset of symptoms, (2) progressive development of focal neurologic signs, (3) rapid mental deterioration preceding the focal symptoms, and (4) persistent or even increasing somnolence with only mild focal signs. The risk of overlook-

(Continued on page A-94)

in
peptic
ulcer

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ing a subdural hematoma is particularly great in patients with a high incidence of cerebrovascular accidents.

ENGLAND

Tubeless gastric analysis—Gastric test-meal examinations are carried out mainly for two purposes. One is to see whether the patient is capable of secreting free hydrochloric acid, as in the diagnosis of pernicious anemia and carcinoma of the stomach. The other is to see whether the patient secretes free hydrochloric acid in excessive amounts or concentrations, as in the study of duodenal ulcer and stomal ulceration. Dr. H. L. Segal and his colleagues (Gastroenterology 29:633, 1955, and other publications) introduced in America a method of tubeless gastric analysis depending on the use of cation exchange resins which are dissociated in the presence of free hydrogen ions in the stomach, so that the cation is absorbed and appears in the urine. Two compounds have been used, both marketed under the trade name DIAGNEX®. Quininium is used as the exchange cation in the one method and azure A dye in the other. Professor L. J. Witts of Oxford and Drs. M. A. Denborough and F. P. Retief (Brit. M. J. 1:1213, 1958) have recently reported their results with the quininium and azure A resins used as screening tests for achlorhydria in 124 patients.

The quininium resin test was compared with the single-dose histamine test meal in the recognition of achlorhydria; agreement was satisfactory. The azure A resin was compared with the augmented histamine test. The results were unsatisfactory, as there was too high a proportion of equivocal results. In addition, false positive and false negative results were more frequent than in the quininium test. The quininium test, in the authors' opinion, is a valuable method of screening patients for achlorhydria, but the azure A method cannot be recommended.

Attempted suicide—A recent report by a joint committee of the British Medical Association and the Magistrates Association advocates that the law of England and Wales be amended to provide that suicide, and, consequently, attempted suicide, should no longer be criminal offenses as such. This excludes cases of suicide pact and incitement to suicide. So far as possible, no case of attempted suicide should be brought before any court except, for example, if there is a breach of the peace. This is the practice in Scotland.

The committee received information from a number of consultants in general and mental hospitals, who were practically all agreed that the person who has attempted suicide is a case for medical and social care, and that intervention of the law is undesirable and unnecessary.

England and Wales, India, and some of the American states are the only places where suicide and attempted suicide are regarded as criminal offenses. In Scotland no police action is taken in most cases and no charge is ever brought on the ground that attempted suicide is in itself a crime. But when circumstances demand it, a charge of breach of the peace is taken. The action of the individual at the time of the incident is not an issue in such a charge, but only the fact that the behavior has been to the breach of the public peace and annoyance or alarm of the lieges. The committee believed that the procedure in Scotland is a proper one and recommended that the necessary amendments should be made to the law in England and Wales to provide that those cases of attempted suicide which must be brought before a court should be dealt with summarily as a breach of the peace. The committee also recommended that careful attention should be paid to the extension of facilities for psychiatric treatment as and when possible.

Complications of steroid therapy—In a recent discussion at the Royal Society of Medicine on this subject, Dr. John H. Glyn pointed out that a review of the world literature revealed startling discrepancies in the reported incidence of side effects occurring during maintenance steroid therapy, figures ranging from 0 to 86 per cent having been quoted for major side effects and from 33 to 100 per cent for all side effects. Successful maintenance therapy ultimately depends on the balance between the susceptibility of the pathologic and the nonpathologic tissues to hormones. This balance is quite impossible to predict in individual patients, but as between different groups it is possible with some confidence to anticipate which will incur the most problems. Case selection should be based not only on these considerations but also on the prognosis if steroid therapy is not given. An-

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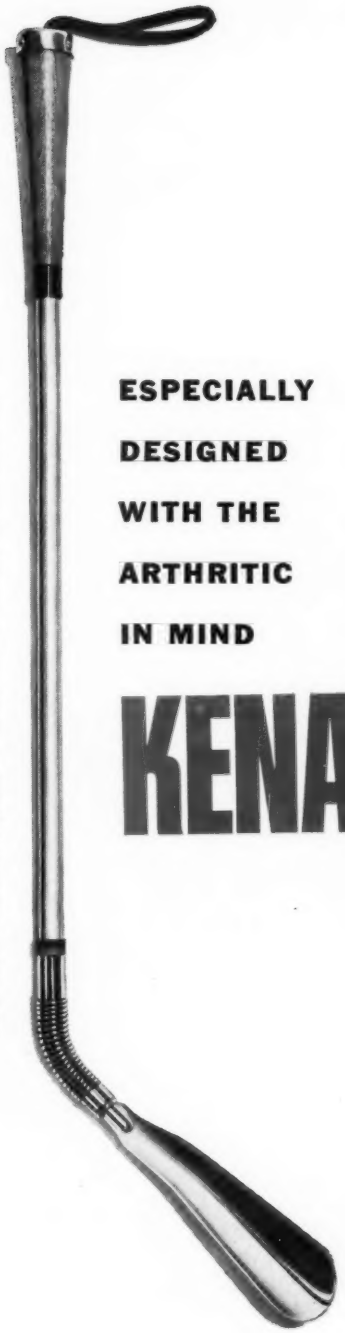

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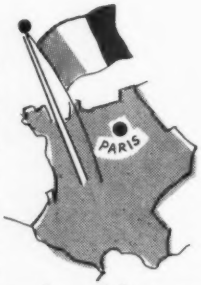
other well-recognized and perplexing fact is that in two successive and apparently identical courses of steroid therapy the same complication does not necessarily develop in a patient. Similarly, it is not safe to predict the type of complication he will have on the basis of susceptibilities he had previously.

Unless a short course of treatment for a specific purpose is planned, the decision to start a patient on steroids is a major one and should never be taken without full consideration of the implications of long-term and possibly permanent suprarenal suppression. Many clinical, sociologic and even economic factors must be evaluated in advance if disappointment and potentially difficult weaning processes are to be avoided. The intelligent cooperation of the patient should be sought, and he should have some of the pros and cons explained to him. A careful base line of objective measurements should be made before treatment commences so that the benefit to him can be accurately evaluated from time to time and the treatment terminated or modified as soon as it seems to be losing its good effect. Above all, these drugs must never be used casually or merely as analgesics.

FRANCE



Fibrinoid and the collagen diseases—Studies carried out in 1957 by Klemperer, Gillie and Craig, Coons and Kaplan, Vasquez and Dixon established that fibrinoid results from conversion of fibrinogen into substances closely related to fibrin. It is not a product of degeneration and is not derived from the collagen fibers or the basic substance. Several varieties of the fibrinoid substance are known; they have different staining affinities and slightly different chemical compositions, but all of them are rich in alpha and beta globulins and serve to strengthen the complete or incomplete antibodies. This fact explains why the collagenoses are included in the group of allergic-immunologic diseases.

Jean De Brux (*La Presse médicale*) believes that fibrinoid is an insoluble derivative of fibrinogen. In the course of inflammatory processes, thromboses are produced. Fibrinoid is deposited in the lumina of the vessels; it exudes through and forms deposits in and around the vessels' walls which the inflammation has rendered more permeable.

Simultaneously, an endothelial proliferation is produced which eventually covers the fibrinoid deposits. The basic substance and the collagen fibers are masked but not destroyed; on histologic study they can be found in the lesions after trypsin digestion has removed the fibrinoid.

Fibrinoid deposits and infiltration of the vessels are seen in both localized and generalized thromboses.

Localized thromboses—These thromboses occur in cases of proliferative and thrombotic endarteritis and in angiomas. In such conditions, the invading fibrinoid obliterates the lumen and thus will delay the final healing until resorbed.

Generalized thromboses—Cancer may cause repeated phlebothrombosis of the migrating type first described by Trousseau in 1862. In addition to thromboses of the great venous trunks, microthromboses also are found at autopsy in the kidneys, spleen, lungs and colon. Clinically, they cause visceral symptoms and attacks of shock. Such thromboses are produced not by metastases, but by the blood's increased tendency to clot due to coagulation in the vessels. This phenomenon is inhibited by heparin.

Thromboses in obstetric cases are produced by thromboplastic substances derived from necrotic ulcers of the fetal membranes and of the placenta; such small necrotic ulcers generally are present in eclampsia. These accidents also resemble Shwartzman's and Sanarelli's phenomena.

Similarly, in cases of thromboses caused by infection or toxic agents, there is a syndrome of generalized clotting of the blood in the vessels which can only be stopped by heparin and similar agents.

Such thromboses are found in all the collagen diseases, predominantly on the serous and synovial membranes and in the lungs and kidneys. They are seen under the endocardium, in the glomeruli, and in the alveoli where they obliterate the capillaries. In the large vessels, the thrombi, which form a crescent-shaped mass occupying a large part of the lumen, become covered with endothelium.

De Brux concludes that the characteristic lesions of collagen diseases do not result from a primary disorder of either the fibrils or the basic connective tissue, but originate from a more widespread disorder: extravasation and coagula-

(Continued on page A-98)

First thought:

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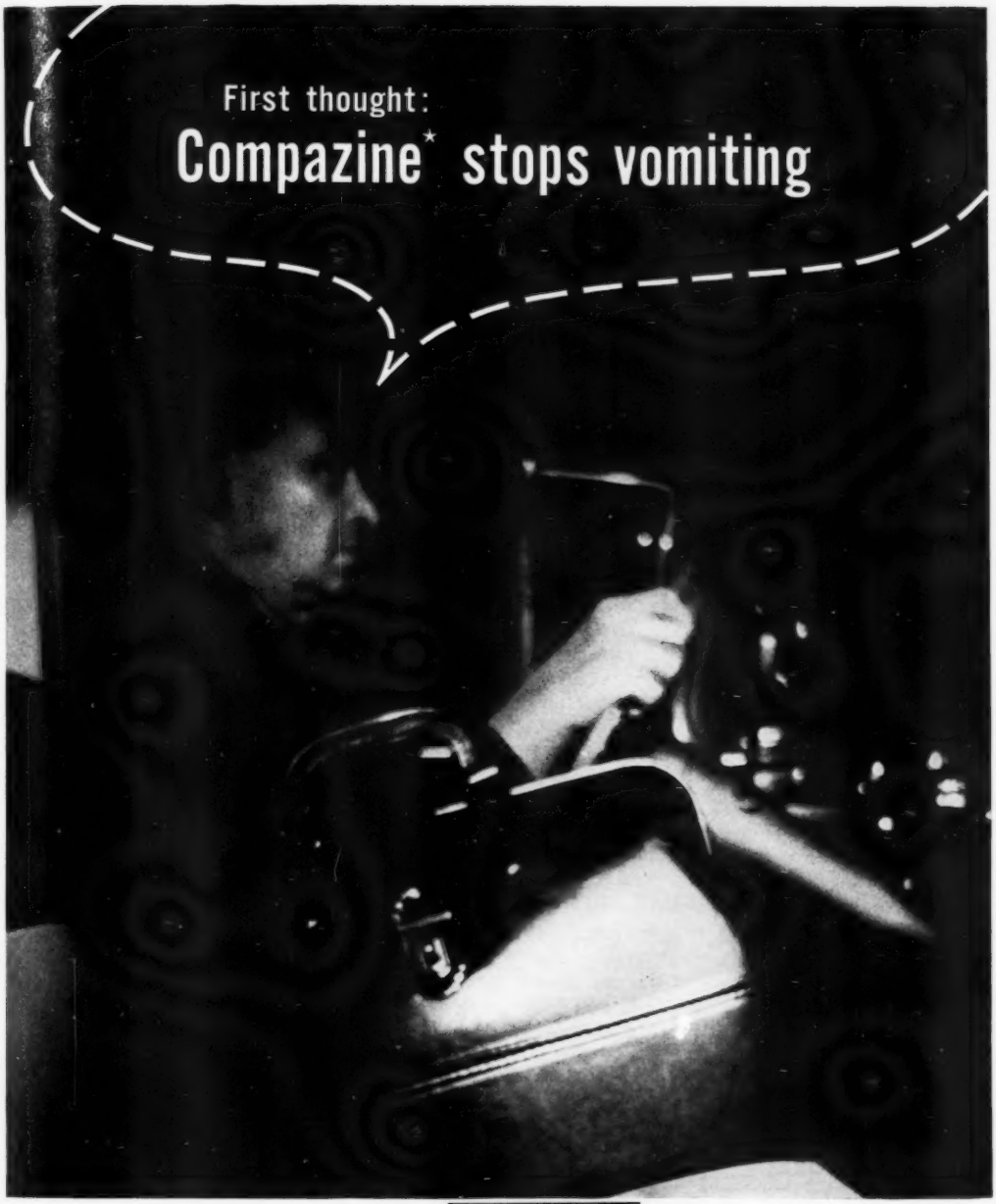

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tion of the plasma with conversion of fibrinogen into an insoluble fibrinoid substance.

In lupus erythematosus, one of the most typical of the collagenoses, the initial lesion seems to be a result of this secondary transformation of fibrinogen in the thrombosing process and of extravasation due to the permeability of the inflamed vessel's walls.

SPAIN

Anatomic technic of roentgenography—At a meeting of the Spanish Medical Society of Radiology, Electrology and Nuclear Medicine, Dr. Fernando Yarza of Saragossa told of his own technic for producing roentgenograms which have the quality of an actual anatomic part. Working first with Darwin R. Craig, a United States Navy photographer who devised the Log-E-Tron method of aerial photography, Dr. Yarza later made a detailed study of other photographic methods, including relievography, which was perfected by Eugenio J. Alvarez of the Radiologic and Physiotherapy Institute of Buenos Aires. Through continued research, Dr. Yarza developed the "anatomic technic," which is inexpensive and easy to use, and gives excellent results.

Utilizing the intermediate positive film of the relievography system as a compensating filter mask, he obtains a negative without relief effects but with surprising clearness of the fine details which are masked in the fuzziness of the dense or grayish zones of the original. A positive film is placed in the copying machine at a distance of 4 cm. in front of the negative, which is in contact with an unexposed x-ray plate. Thus, the positive film is between the light and the negative, and a reproduction is obtained which has perfectly balanced values and shows every detail in the x-ray plate. In copying the original roentgenogram, each part of the plate receives exactly the quantity of light necessary to unify the impression and obtain the maximum values. It is therefore possible to unite in one reproduction the series of effects which can be obtained from any roentgenogram by varying the amount of light through which the various portions are viewed. Further, by the simple method of superposing the positive and negative films separately, it is possible to achieve the light compensation necessary to obtain the full value of the roentgenogram without the light parts being fogged or the more strongly exposed parts being underexposed.

The results obtained by this method are superior to those presented by Drs. Jutras and Fishgold in their book on the Log-E-Tron system. Moreover, the technic does not require either a specially trained operator or special apparatus.

Surgical treatment of deafness—A postgraduate course on the surgical treatment of deafness was recently presented at the Madrid Medical School under the direction of Dr. Guillermo Nuñez Pérez. The course included lectures on the value of audiometric exploration in determining the degree and quality of deafness before operation. In addition, the students attended operations demonstrating the various surgical technics. At the closing session Dr. Nuñez presented a paper on "Present status of surgery for deafness," in which he traced the evolution of the different surgical technics. At present the principal methods used are: labyrinthine fenestration or the formation of a small aperture which permits passage of the sound waves; mobilization of the stapes or liberation of the adhesions from the window where it is joined; and tympanoplasty or placing of free grafts to repair loss of the tympanic membrane or elements of the middle ear, including loss of part of the chain of ossicles.

Even with the many advances in surgical technics and the highly successful results attained in some cases, there are certain types of deafness which cannot be alleviated by surgery. Nevertheless, although the technics used are still under study and revision, there has been an increase in the number of deaf people who have regained auditory function.

International Association for Bronchial Studies—More than 300 members from all parts of the world are expected to attend the eighth annual meeting of the Association to be held in Madrid in the spring of 1959. The following Spanish physicians attended the seventh annual meeting held recently in Munich: Dr. Manuel Tapia Martínez, president of the Association's Spanish section; Dr. José Alix, who read a paper prepared by Dr. Carlos Jiménez Díaz; Dr. F. Blanco Rodríguez, who presented an original classification of congenital diseases of the bronchia and lungs; and Dr. Soler Jorro.

Postgraduate Medicine

SPECIAL ISSUE

Therapeutics

SEPTEMBER 1958

FOREWORD

THIS issue of POSTGRADUATE MEDICINE is devoted primarily to articles concerned with the treatment of disease. The physician's armamentarium has been vastly increased, particularly during the last half century, with the development of endocrine products, the antihistamines, blood derivatives, drugs pinpointed to various areas of the nervous system, and a vast array of hypnotics, sedatives, tranquilizers, vitamins and special products in the field of nutrition. Those who are historically minded and sufficiently old to remember may well compare what was available before 1910 with what has become available since that time.

Therapeutics is concerned with the treatment of disease. The word derives from Greek terms meaning a slave or an attendant; it became a term for those who attended the sick and was finally extended to mean a remedy or a cure. The common use of the words "therapy" and "therapeutics" began in the early part of the nineteenth century. Sir William Osler believed that the father of therapy was probably Celsus, who wrote the following:

> Some of the sick on account of their eagerness took food on the first day, some on account of loathing abstained; and the disease in those who refrained was more relieved. Some ate during a fever, some a little before it, others after it had subsided, and those who had waited to the end did best. For the same reason some at the beginning of an illness used a full diet, others a spare, and the former were made worse. Occurring daily, such things impressed careful men, who noted what had best helped the sick, then began to prescribe them. In this way medicine had its rise from the experience of the recovery of some, of the death of others, distinguishing the hurtful from the salutary things.

In an essay called "Teaching and thinking," included in his collected essays under the title "Aequanimitas," written in 1894, Osler began to express his skepticism if not therapeutic nihilism. Here are a few quotations:

> It took the profession many generations to learn that fevers ran their course, influenced very little, if at all, by drugs, and the £60 which old Dover complained were spent in drugs in a case of ordinary fever about the middle of the last century is now better expended on a trained nurse, with infinitely less risk, and with infinitely greater comfort to the patient. . . .
>
> With diminished reliance upon drugs, there has been a return with profit to the older measures of diet, exercise, baths and frictions, the remedies with which the Bithynian Asclepiadae doctored the Romans so successfully in the first century. Though used less frequently, medicines are now given with infinitely greater skill; we know better their indications and contraindications, and we may safely say (reversing the proportion of 50 years ago) that for one damaged by dosing, one hundred are saved. . . . But know also, man has an inborn craving for medicine. Heroic dosing for several generations has given his tissues a thirst for drugs. As I once before remarked, the desire to take medicine is one feature which distinguishes man, the animal, from

his fellow creatures. It is really one of the most serious difficulties with which we have to contend. Even in minor ailments, which would yield to dieting or to simple home remedies, the doctor's visit is not thought to be complete without the prescription.

One wonders how Osler might have modified these views had he lived to witness the full flower of the amazing results accomplished by hormones, vitamins, antibiotics, vaccines and the multitudinous analgesics and anesthetics. He would, of course, have welcomed them and he would no doubt have emphasized even more the tremendous responsibility that rests on the physician in choosing wisely as to when to begin treatment, the dosages of the drugs to be used, and when to stop treatment. Indeed his philosophy of therapy is reflected repeatedly in some of the important articles which appear in the symposium on therapy which constitutes this issue of POSTGRADUATE MEDICINE. In his article "Medicines, miracles and mischief," Dr. Jesse D. Rising says, "Modern chemistry and technology have made available countless agents of proved or potential therapeutic usefulness. The availability of these medicaments imposes increased responsibility on the physician who must provide his patient with every possible relief from suffering and disease and at the same time must administer nothing deleterious or destructive."

Similarly, Drs. William H. Bachrach and Melvin Brody in their contribution on "Cholinergic and anticholinergic drugs" warn, "Anticholinergics as the sole treatment of peptic ulcer are not only ineffective but they may also be dangerous."

Regarding the use of hypotension-inducing drugs and their relation to hypertension, Dr. Arthur Grollman concludes: "Not until it is possible to counteract the basic derangement responsible for the elevation in blood pressure can any therapy be considered truly rational."

In considering "Analgesic agents and the control of pain," Drs. E. G. Gross and H. H. Keasling comment as follows: "The title of this article implies that analgesic agents are but one method to be utilized in the control of pain. We agree with this thesis completely."

Perhaps what Dr. A. Ross McIntyre says in his discussion of "Curariform drugs and the new hypothesis concerning neuromyal transmission" could apply to every aspect of modern therapy. Similarly Drs. Mark Nickerson and Peter E. Dresel in their article "Adrenergic drugs and their antagonists" conclude: "Sympathomimetics and adrenergic blocking agents are useful and effective drugs if employed with intelligence, understanding and flexibility."

These quotations should not be considered in any way deprecatory to the use of the many products already available to the medical profession or of new drugs likely to appear within the next few years. Many hundreds of new drugs and new preparations are now launched annually, among which physicians must choose on the basis of the information that comes to them through detail men, direct-mail pamphlets and brochures, some hundreds of pounds of samples, and the hundreds of periodicals free and by subscription that are available to them. The physician will learn most in each instance, as he has done in the past, by his own observations of the effects he is able to secure in his own practice. But he will not experiment unwisely on his patients, keeping in mind the observations made by Dr. M. J. Schiffrin in his contribution on "Ethics and new drugs," which also appears in this issue of POSTGRADUATE MEDICINE and which will aid the physician to formulate his own philosophy in the employment of new remedies. "Experimentation in its broadest sense must be practiced by all physicians engaged in the art and science of medicine."

MORRIS FISHBEIN

Medicines, Miracles and Mischief

JESSE D. RISING*

University of Kansas Medical Center, Kansas City

JESSE D. RISING

THE physician, like the clergyman, is accustomed to suffering the barbs of the occasional disgruntled and dissatisfied individual, but his usual role is that of a benefactor of mankind accepting with suitable modesty the plaudits of his fellows. He is heir to the oldest of the priestly traditions and is accorded a respect and awe unique in our culture. His infallibility, while far from absolute, remains the ideal of the laity at an emotional if not at an intellectual level. Failure on his part to live up to the ideal evokes a reaction of rejection and unreasonable hostility, but this does not change the image of the physician as a benefactor of humanity.

From this position of prestige—yes, of power over the lives and even the souls of his fellows—the healer has, from time immemorial, faced the necessity of scrutinizing his methods and motives lest he be false to his tradition and use his gifts foolishly or for evil purposes. Modern chemistry and technology have made available countless agents of proved or potential therapeutic usefulness. The availability of these medicaments imposes increased responsibility on the physician, who must provide his patient with every possible relief from suffering and disease and at the same time must administer nothing deleterious or destructive. This is a difficult situation because potentialities for evil reside in even the most benign drug. The fact that we have no clear definition of the limits of a physician's responsibilities increases the difficulty. Are they limited to the welfare of the individual? The family? The village, city or state? What of his position relative to the larger, biologic framework? Shall it be said of him as it was of the politician, "The only result of your progress . . . will be that in a few generations there'll be a real revolution—a natural, cosmic revolution. You're upsetting the equilibrium. And, in the end, nature will restore it . . ."?[1]

As a student of biologic progress (evolu-

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tion has so perceptively pointed out, "Man is the only creature that is capable of disliking the creation . . . in his ardor to reform and recolor what is intrinsically not so good, he tends to overlook what is intrinsically not so bad."[2] He "is the one creature who can significantly alter himself and his environment to suit his private tastes . . . who can know very much about himself . . . who can dodge many harsh and dangerous exactions of Nature only to run foul of harsh and dangerous devices of his own manufacture."[3] "When Nature gave him a brain and with it the unprecedented privilege of contributing to the arrangement of his own life, she included the less enviable capacity of suffering for his own mistakes."[4]

We must recognize the effects of medicine on human genetics, realizing that "the long-term influence of our modern advances in medicine and of all our artificial aids to life must gradually decrease the biologic fitness of the population. This happens by the ever-increasing accumulation of all sorts of mutations that, under more severe conditions, would have been eliminated. Since new mutations keep occurring in every generation and are thereafter handed down unless some descendant dies of his disability, these mutations will tend to accumulate until the population is bearing as great a load of them as can be kept alive by its greatly enlarged cohorts of doctors, exercising their best medical skill and working overtime. Moreover, the more we add to the naturally occurring mutations by producing others by means of atomic radiation or medical x-rays, the sooner this eventuality will materialize."[5]

Man's tampering with the balance of nature, even with the best of intentions, has very commonly led to unhappy results. Physicians and engineers have contributed their share to the imbalance of nature and have made it possible for vast numbers of human creatures to inhabit small portions of this planet.

In contrast with the situation which existed in the comparatively recent past when hope and palliation were all that the physician could offer, the modern therapeutist has at his disposal an ever-increasing array of specific or quasispecific agents. His attitude toward them, his professional knowledge and integrity, his philosophy—all of these will determine whether, in the final analysis, he will apply them so as to assure the full realization of their beneficent potentialities while minimizing the chances of harm, present or remote. He must always bear in mind the fact that even good medicine is at best the lesser of two evils.

Drugs have toxic actions and physiologic side effects which often are predictable on the basis of their pharmacologic actions or can be explained as hypersensitivity reactions. Recently a different group of reactions to medication has attracted attention, reactions that we cannot, in our present state of knowledge, place in either of these groups. These reactions present the appearance of actual disease states, mimicking diseases which have been known for some time. The following are a few interesting examples.

Hydralazine Syndrome

One of the most dramatic examples of this type of drug response is what is sometimes called the hydralazine (APRESOLINE®) syndrome, which comprises two types of illness. The first is rather typical rheumatoid arthritis complete with all the expected laboratory findings. The more severe form is less common and is very nearly identical with acute disseminated lupus erythematosus including the presence of a biologic false-positive reaction for syphilis and the L.E. cell phenomenon.[6-11] The outstanding difference between typical acute disseminated lupus and the severe form of hydralazine syndrome is the tendency for the latter to improve when the drug is discontinued, but this is not invariably true as some of the patients require treatment with ACTH and cortisone. Hydralazine syndrome has been produced in 8 to 10 per cent of patients treated intensively for several months.

Hexamethonium and Pulmonary Fibrosis

Numerous difficulties have attended the use of ganglionic blocking agents in the treatment of severe hypertension, but one interesting reaction has received scant attention. In a num-

ber of patients with severe hypertensive disease treated with hexamethonium (with or without hydralazine) a dramatic type of respiratory disturbance has developed, characterized by a rather sudden onset of dyspnea, cyanosis, fever, cough and chest pain. It may lead to death in one month. There is no certain knowledge of the cause of this reaction, but it is thought that the lesions are the result either of attacks of left ventricular failure modified by intermittent hypotension or of a pulmonary collagen disease. Pathologically there is acute diffuse interstitial pulmonary fibrosis which is like the changes found in patients having the Hamman-Rich syndrome and resembles pulmonary scleroderma.[12,13]

Mecamylamine Chorea

Because of the inadequacy of our present forms of treatment of hypertension it is not surprising that ganglionic blocking agents continue to receive considerable attention. One of the promising new drugs is mecamylamine (INVERSINE®) which, because it is a secondary amine instead of a quaternary amine, penetrates cells more efficiently than the other ganglionic blocking agents and is consistently and completely absorbed from the gastrointestinal tract. The improved gastrointestinal absorption gives it an obvious advantage over other agents, but it has been postulated that the very feature responsible for this pharmacologic triumph may permit the drug to enter cells in the central nervous system where its effects may not be desirable. Neurotic reactions characterized by anxiety or depression (or a mixture of these symptom complexes) have developed while patients were being given mecamylamine, and it is probable that mecamylamine has been a factor in the production of some major psychoses.[14] Several patients have had neurologic reactions similar to chorea. Some have had marked jerking and intention tremor and have impressed observers as having a condition reminiscent of Huntington's chorea, while others have exhibited the queer, purposeless, irregular movements of the extremities, face and body characteristic of Sydenham's chorea. Slurred speech, dysphagia and dysarthria have been reported, and when these symptoms are combined with intention tremor, it could be difficult to differentiate the condition from multiple sclerosis. In addition, some patients have exhibited grand mal epilepsy while taking this medication.[15]

Rauwolfia, Ulcers and Suicide

We all remember when *Rauwolfia* and its products were introduced as extremely safe, if somewhat mild, antihypertensive drugs. At that time their sedative properties were recognized and the opinion was general that we had at last an extremely safe calmative agent to take the place of phenobarbital. It is to be hoped that no physician remains of this opinion, for reserpine is certainly one of the most dangerous of the tranquilizers and probably has very few indications as a psychotherapeutic drug except in the psychiatric hospital.

Soon after the introduction of *Rauwolfia* into human therapeutics it was noted that the incidence of peptic ulcer in patients who received *Rauwolfia* products far exceeded what one could reasonably expect on the basis of chance. The pharmacology of the drug would, indeed, lead one to expect that this complication might result because it has parasympathomimetic (vagal) effects. We now know from human and animal experiments that both oral and parenteral reserpine increase the secretion of gastric acid, and there remains little doubt that the drug can at least precipitate latent or potential peptic ulcers.[16]

Psychic depression is commonly observed in patients who are on reserpine therapy, and the literature contains numerous reports of severe psychotic reactions. Most of them resemble the depressive phase of manic-depressive psychosis but some are characterized by agitation or paranoia with suicidal tendencies. Numerous suicides have been reported, and many physicians have knowledge of unreported cases. We can only speculate about the frequency of severe psychologic reactions, but when one considers the documented incidence of emotional reactions as compared with the drug's inefficiency as an antihypertensive agent, one is reluctant to accept it as a routine medication for treating hypertension.[17-19]

Reports of edema and congestive heart-

failure precipitated by reserpine (and alseroxylon) in patients with hypertension but without a previous history of cardiac decompensation further demonstrate the need for caution. In one series, cardiac decompensation with ankle edema developed in five cases shortly after the institution of therapy, and some of these patients had exertional dyspnea and basilar rales. Furthermore, only one of the five patients had significant lowering of the blood pressure. None of them improved until the drug was discontinued; all responded promptly after it was withdrawn.[20]

In addition, there is good evidence that *Rauwolfia* is sometimes responsible for the production of ventricular premature contractions in patients with organic heart disease and high blood pressure.[21]

Phenothiazine Tranquilizers, Parkinsonism and Hepatitis

The phenothiazine tranquilizers include chlorpromazine (THORAZINE®), promazine (SPARINE®), mepazine (PACATAL®) and prochlorperazine (COMPAZINE®). They have so many pharmacologic actions that it is surprising that they do not cause more undesired side effects than they do. Pertinent to this discussion is the fact that these drugs quite frequently cause an extrapyramidal syndrome that is often indistinguishable from parkinsonism, with generalized cogwheeling, rigidity, tremor, pill-rolling motion of the fingers, mask facies, skin changes, attitude of flexion, gait disturbances, drooling and poverty of movement. The intensity of the extrapyramidal reactions seems to bear a direct relationship to dosage, and the individual drugs differ in their tendency to cause parkinsonism. The symptoms subside rather slowly after the drug is stopped and may persist for two or three months.[22]

It is well known that chlorpromazine occasionally causes jaundice, but the erroneous notion is prevalent that this jaundice is invariably benign and of an obstructive nature. There is clear evidence that hepatocellular damage is rather common.[23] Severe jaundice has been reported to follow a single relatively small dose of the drug,[24] and there is good evidence that chlorpromazine can cause clinical hepatitis in the absence of icterus (anicteric hepatitis).[25]

Syndromes Caused by Adrenocortical Hormones

Cortisone, prednisone and prednisolone so frequently produce peptic ulcer disease that some manufacturers have incorporated antacids in preparations of some of these hormones. This is a pharmacologically irrational approach to the problem; it gives the physician a false sense of security without materially decreasing the incidence of peptic ulcer. Peptic ulcers associated with corticoid therapy are frequently asymptomatic until massive hemorrhage or perforation occurs. In this respect they differ from the usual picture of the disease. Even perforation may cause relatively few symptoms, and the patient may have extensive peritonitis before there are indications of illness. This is indeed a high price to pay for the benefits to be derived from treatment, especially if the condition calling for the use of the hormone is a relatively benign one, as is so often the case.[26]

A frequent result of corticoid therapy is euphoria, which would be welcome were it not for the fact that it indicates affective changes which may lead to frank psychotic episodes. Some of these reactions take the form of a manic-depressive psychosis and may be characterized by excessive elation on the one hand or severe depression on the other; others imitate more or less typical schizophrenic behavior patterns.

In more than a few patients, grand mal epilepsy has developed during corticoid therapy, and, while it appears that persons with abnormal electroencephalograms more often are the victims of this type of reaction, a normal tracing is no guarantee that the patient will escape. Grand mal seizures are especially frequent among children.[26,27]

Corticoids are commonly used in the treatment of arthritic conditions, and one must never forget that these hormones are prone to cause osteoporosis. This complication is most troublesome in elderly individuals and may intensify their orthopedic problems. The weakening of the bones may lead to spon-

taneous fractures in postmenopausal women.

Collagen diseases are among the leading indications for corticoid therapy, but the question has been raised whether the hormones may occasionally precipitate systemic lupus erythematosus and periarteritis nodosa as reported in 18 of 128 patients who presented clinical features of hypercortisonism. It may be argued that these patients actually had systemic lupus erythematosus or periarteritis nodosa rather than rheumatoid arthritis, but the patients tended to revert to a rheumatoid arthritis syndrome when hormones were withdrawn and the hypercortisonism relieved.[28]

A source of trouble that has often been overlooked is the shortening of coagulation time in patients who are on corticoid therapy, but reports indicate that there is a high incidence of thrombo-embolism, including pulmonary embolism, in patients being treated with adrenocortical steroids.[29, 30]

Acetazolamide and Ammonia Intoxication

Acetazolamide (DIAMOX®) is a mild diuretic which is frequently given to cardiac patients in order to decrease their requirements for the more potent mercurials. It is an inhibitor of carbonic anhydrase, which normally makes hydrogen ions available for exchange with sodium ions in the glomerular filtrate and for the formation of ammonium ions from ammonia by the renal tubular cells. It is well known that severe acidosis may develop in patients who receive acetazolamide with ammonium chloride because of their inability to excrete the excess chloride ion. Ammonia intoxication may develop spontaneously in patients with passive congestion of the liver secondary to congestive heart-failure, and both ammonium chloride and acetazolamide have been implicated as etiologic factors in hepatic coma in this type of patient.[31]

Antibiotics and Severe Enterocolitis

Antibiotics have been one of the greatest boons ever given to mankind. Their beneficial nature has been obvious to all, but they have been responsible for the whole spectrum of ordinary drug reactions. They can also cause one especially important and dramatic therapeutic syndrome, pseudomembranous enterocolitis. This has been a recognized entity for many years, and a number of cases have been reported in the literature; but with the advent of antibiotic therapy—specifically, therapy with the broad-spectrum agents that destroy the normal intestinal flora—there has been a tremendous increase of this deadly disease. It is impossible to estimate how many patients have been stricken with this condition which is usually iatrogenic.[32, 33]

Cycloserine Fits

Cycloserine is one of the newer antibiotics which shows promise of being helpful in the treatment of patients with intractable tuberculosis. The dosage of this drug must be regulated very carefully because it has a narrow therapeutic range, and even a slight overdose precipitates grand mal seizures in a high percentage of patients. Electroencephalograms have not helped to predict which patients will have epileptiform seizures. Neurotic, psychotic and personality changes have also been reported. The drug is especially dangerous for patients who have diminished renal function, as it is excreted by the kidneys, and is retained in toxic amounts due to renal damage.[34]

Isoniazid Neuritis

Isoniazid is one of the most important of the agents used in the treatment of tuberculosis. Shortly after it was introduced there were reports of euphoria and psychotic reactions, but it is now believed that the euphoria is directly related to the actual clinical improvement of the patient and that the drug does not cause psychotic reactions. A typical peripheral neuropathy has, however, been reported. This complication evidently is related to the dosage of the drug employed and apparently affects adults exclusively. Symptoms include paresthesias, numbness, burning pain and weakness, and the patients exhibit hypesthesia and either exaggerated or absent deep tendon reflexes. This neuropathy resembles the natural and experimental neuritis caused by deficiency of pyridoxine, and the consensus is that isoniazid functions as an antimetabolite

against pyridoxine. Early in its course the neuritis responds to pyridoxine therapy, but if it is permitted to progress it tends to become permanent.[35]

Congenital Deformities

Physicians now face the horrible possibility that they, in addition to certain "acts of God," are responsible for many developmental defects including cyclopia, dextrocardia, Siamese twins, congenital cardiac anomalies, cleft palate—and, yes, even mongolism. How can this be? It is increasingly apparent that many agencies, some of them applied by physicians, can be responsible for developmental defects. Hypoxia during a crucial period of gestation is probably a potent cause of trouble and may be produced by deep anesthesia in addition to shock, anemia and external trauma which injures the placenta and thereby interferes with the oxygen supply of the embryo.

It is well known that rubella during the first trimester of gestation is likely to deform the embryo, but it is less well known that x-ray, cortisone and corticotropin (ACTH) are probably also teratogenic. They have been shown to be in experimental animals. It is a sobering thought, but physicians must be ready to accept responsibility for the "regrettable consequences" of their ministrations to the expectant mother as well as to take credit for the happier ones. In this light purposeless meddling cannot be condoned.[36-38]

Conclusion

The thoughtful physician will use drugs with the full realization that in doing so he is taking a calculated risk, weighing the chances for cure or relief against the ever-present possibility that harm may be done. He will not lightly prescribe medications, but will exert every effort to understand the sites and mechanisms of the actions of drugs and the harmful effects that may result from their use.

Caution is especially necessary in the use of newer drugs. This is not to say that one should stubbornly deny his patients the benefits of medications that are not fully understood. One should, however, recognize the gaps in his knowledge. Scientists inevitably accumulate facts faster than understanding; one of our obligations is to realize this and exert our individual and collective efforts toward advancing understanding. We can never know all that we should like to, and "very few of those who have followed the history of medicine, from the first trepanning operation to the modern transplantation of the cornea, would agree that we should have abandoned medicine because at each stage in its history first attempts at operations have been unsuccessful. A little learning, if it is the first learning, is the way in which men move on to new knowledge, and it can be regarded as dangerous only when the practitioner or patient overestimates it. . . . Learning is not dangerous because there is only a little of it, but it is dangerous not to know just how little there is."[39]

We shall continue to experiment and try new drugs; therapeutic miracles will follow one another at an increasing rate. Will we pay too high a price for this progress? Will we sacrifice human beings unnecessarily? The answer depends on the medical profession as a whole and, even more important, on the individual physician. "Man is a prober and a meddler, and in this, so long as he holds true to his own gifts, he will not stop."[40] Among the physician's gifts must be the ability to grasp broad concepts, to reflect and ponder, to advance from the first learnings to new, more complete knowledge and understanding. In a word, he must employ therapeutic agents with wisdom, in such a way as to assure the realization of maximal benefits, exercising all the reasonable precautions against the occurrence of undesirable effects and iatrogenic syndromes. He must produce miracles without mischief—a superhuman task facing the one man in our culture who is conceded superhuman powers.

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Hypnotics and Sedatives

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SEVERAL of the so-called tranquilizing or ataractic drugs possess sedative properties and a few exhibit hypnotic activity. However, until pharmacologic definition in this area is better, it is wise to limit any discussion of hypnotic and sedative agents to those that conform to definitions that are accepted.

Hypnotic and sedative agents are employed to produce a depression of the central nervous system short of unconsciousness. Hypnotics suppress cerebral activity sufficiently so that the patient is less aware of his environment and conditions favorable for sleep are established. Sedation is less profound; elevation of the threshold of irritability of the central nervous system is less than that required to result in sleep. Sedation, hypnosis and general anesthesia differ primarily with respect to quantity of effect. Sedatives or hypnotics can produce loss of consciousness and death as a consequence of central depression if sufficiently large doses are administered.

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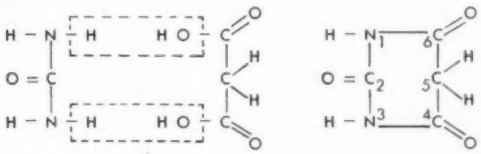
We may group the sedative and hypnotic drugs in two categories for discussion, the barbiturates and the nonbarbiturates.

Barbiturates

Barbiturates are classified chemically as derivatives of barbituric acid, which is a condensation product of urea and malonic acid.



Urea Malonic acid Barbituric acid

For hypnotic activity, substitution of both hydrogen atoms at the 5 position is required. A few derivatives, employed largely as anticonvulsants in the symptomatic treatment of epilepsy, possess an additional substituent on one of the nitrogen atoms. When thiourea rather than urea is condensed with malonic acid, thiobarbituric acid results; derivatives of this compound are termed thiobarbiturates. Inasmuch as these agents are employed almost exclusively for anesthesia, I will refer to them here only as information concerning them pertains to the barbiturates.

The barbituric acid derivatives are only

TABLE 1

OFFICIAL AND N.N.D. BARBITURATES

BARBITURATE	PROPRIETARY NAME	AVERAGE ORAL HYPNOTIC DOSE FOR ADULTS (GRAMS)
Long duration of action (six or more hours):		
Barbital N.F.	VERONAL®	0.3-0.5
Mephobarbital N.F.	MEBARAL®	*
Phenobarbital U.S.P., N.F.	LUMINAL®	0.1-0.2
Intermediate duration of action (three to six hours):		
Amobarbital U.S.P., N.F.	AMYTAL®	0.1-0.3
Aprobarbital N.F.	ALURATE®	0.065-0.13
Butabarbital N.N.D.	BUTISOL®	0.045-0.2
Butallylonal N.F.	PERNOSTON®	0.2
Butethal N.F.	NEONAL®	0.1-0.2
Diallylbarbituric acid N.F.	DIAL®	0.1-0.3
Metharbital N.N.D.	GEMONIL®	*
Pentobarbital U.S.P., N.F., N.N.D.	NEMBUTAL®	0.1-0.2
Probarbital N.F.	IPRAL®	0.1-0.2
Vinbarbital N.F.	DELVINAL®	0.1-0.2
Short duration of action (less than three hours):		
Allylbarbituric acid N.F.	SANDOPTAL®	0.2-0.4
Cyclobarbital N.F.	PHANODORN®	0.1-0.3
Heptabarbital N.N.D.	MEDOMIN®	0.2-0.4
Secobarbital U.S.P., N.N.D.	SECONAL®	0.1-0.2
Ultrashort duration of action (minutes to hours, depending on dose):		
Hexobarbital N.F.	EVIPAL®	†

*Usually employed as an anticonvulsant for the treatment of epilepsy in a dose of 0.1 to 0.8 gm. per day.

†Employed primarily as an intravenous anesthetic.

slightly soluble in water, but water-soluble compounds are formed with alkalies (sodium, calcium, magnesium, and so on). Solutions of these salts are strongly alkaline, a fact that one should consider when contemplating administering them parenterally.

The official barbiturates and those which are listed in "New and Nonofficial Drugs" are presented in table 1 along with their proprietary names and the usual hypnotic doses. To avoid confusion and in the best interest of his patients, the physician prescribing these agents would be well advised to employ the official or N.N.D. nomenclature.

Actions of the Barbiturates

Central nervous system—The outstanding effects of the barbiturates that find practical application are on the central nervous system. Their depressant actions at this site are much like those of the hydrocarbon anesthetics of the aliphatic series. The character of the depression that one compound induces is much the same as that of the next, but there are differences in potency, duration of action, and time required for the effect to become manifest. As will be noted in table 1, certain compounds are employed for specific purposes, e.g., intravenous anesthesia and symptomatic treatment of epilepsy. The degree of depression and, to some extent, the rate of onset and duration of action depend on the route of administration, the dose, and the compound employed. As one might anticipate, the level of irritability of the central nervous system as well as environmental factors also influence the hypnotic and sedative actions. The mechanisms of these actions are not completely clear. It has been suggested that barbiturates decrease the number of electric changes

that sensory impulses are capable of producing in the cortex in a given period; in other words the higher centers in the central nervous system become less responsive to afferent stimuli. Thus there is less awareness of the environment and sedation or sleep results. A concept placing the site of action in the diencephalon rather than the cortex is somewhat more widely accepted. Recent studies[1] to determine the effect of pentobarbital on spontaneous activity of various diencephalic and mesencephalic structures have led to the suggestion that the barbiturates act predominantly on multineuronal pathways in this area. Unfortunately this neurophysiologic observation, much like others, is more descriptive than explanatory.

The hypnotic effect of orally administered barbiturates appears in from 15 or 20 minutes to an hour. Unless compounds with a long duration of action are given, sleep ordinarily is dreamless, restful and without a subsequent hang-over. Sedative doses are capable of impairing the functional capacity of the central nervous system.[2] One-tenth gram of pentobarbital sodium administered orally interferes with the performance of certain psychophysiologic tests for as long as four hours, with some effects persisting up to 14 hours. Small doses of a barbiturate may significantly affect cortical inhibitory centers which operate as restraining mechanisms. In persons with mental abnormalities, motor and oral activity as well as social interaction are enhanced after the administration of a relatively small amount of secobarbital or amobarbital.[3]

Electroencephalographic changes produced by barbiturates have been adequately described. Small doses having minimal psychic effects usually result in the appearance of "brain waves" of "fast" activity or an increase in beta activity. After hypnotic doses a characteristic sleep pattern (dominant slow rhythms and spindles) is seen. Abnormalities characteristic of cortical depression may be observed for a long period, even when other evidence of action has disappeared; in babies whose mothers received secobarbital such effects have been noted for as long as three days post partum.[4]

In sufficiently large doses, barbiturates will induce anesthesia. The ultrashort-acting compounds are injected intravenously for this purpose. The antiepileptic activity of certain barbiturates is well established and is related to their capacity to elevate the threshold of nerves to various stimuli. The underlying mechanisms of such an effect are not known. Although barbiturates are not analgesic in the sense that they can elevate the pain threshold, there is evidence[5] that they can effectively control postoperative pain in a significant percentage of patients. It has been suggested that the analgesia in such situations is the result of a reduction in concern about the pain rather than any reduction in pain perception. Interneuronal depression at the level of the spinal cord as a consequence of administration of small doses of the barbiturates can be demonstrated, and with sufficiently large doses all spinal reflexes are markedly suppressed.

Respiratory system—In the hypnotic dose range, barbiturates depress respiration only slightly, similar to the depression seen in natural sleep. Progressively more profound impairment of respiratory activity occurs with larger doses. Rate, depth and minute volume are affected in a similar manner. The respiratory effects of barbiturates are attributable for the most part to direct action on the medullary respiratory center. Recent evidence indicates that respiratory rhythmicity disappears prior to the time when the respiratory center becomes inexcitable.[6] However, marked depression of this center may occur without significant impairment in activity of the vasomotor center. Sino-aortic receptors are less sensitive to the barbiturates than is the respiratory center, and respiration may be maintained in the face of depression of the center by the stimulant effect of an associated anoxia on these peripheral mechanisms. It follows that in severe poisoning the administration of pure oxygen may enhance the respiratory depression by removing this stimulus.

The findings of Burstein and Rovenstine[7] have led to the wide belief that anesthetic doses of barbiturates may cause hyperactivity of the laryngeal reflexes and laryngospasm. More recently the effects of pentobarbital and thio-

pental on the activity of the muscles of the glottis have been studied experimentally;[8] an increase in the responsiveness of the laryngeal musculature was not noted after the barbiturates. These observations cast some doubt on our earlier concepts concerning the propensity of barbiturates to produce laryngeal spasm.

A further effect of the barbiturates on the respiratory system is not uncommonly seen in acute intoxication. Pulmonary edema may add to the respiratory embarrassment, and when the longer-acting compounds are involved hypostatic pneumonia may ensue.

Cardiovascular system—In sedative or hypnotic doses the barbiturates do not significantly affect the cardiovascular system. Changes that do occur are similar to those seen in natural sleep. In large doses they are capable of depressing the vasomotor center, and peripheral vasodilatation and hypotension can result. This, coupled with a direct effect on vascular smooth muscle and widespread dilatation of the capillary bed, can cause shock in acute intoxication. Light barbiturate anesthesia may increase cerebrovascular resistance and decrease blood flow through the brain.[9]

Barbiturates in therapeutic dosage do not adversely affect the myocardium, and even though a negative inotropic action can be demonstrated in vitro, the concentrations required are significantly greater than any that might be realized prior to respiratory paralysis in vivo. Some workers[10] have claimed to have noted a decrease in cardiac output following oral administration of a barbiturate in a dosage somewhat greater than a hypnotic one, whereas others[11] have described only an elevation of arterial pressure attributed to an increase in peripheral resistance.

Electrocardiographic abnormalities have been observed following the administration or ingestion of relatively large amounts of barbiturates, but evidence[12] indicates that these changes (flattened or inverted T waves, depressed S-T segments, high P waves) are the result of an associated myocardial oxygen deficit. In this connection it is noteworthy that in dogs the incidence of ventricular fibrillation during hypothermia is significantly less with pentobarbital anesthesia than with ether or cyclopropane anesthesia.[13]

Autonomic nervous system and peripheral nerves—The barbiturates do not affect all autonomic functions in the same manner, and qualitative differences exist among the various compounds. They have little or no effect on chemoreceptor activity,[14] and the different barbiturates effect varying degrees of depression of vasomotor reflexes of carotid sinus origin. Likewise the various derivatives of barbituric acid modify the peripheral cardiac action of the vagus differently. This effect in mammals is characterized by depression or blockade of peripheral vagal ganglia.

Experimental evidence suggests that the barbiturates may affect nerve endings as well as ganglia and that such postganglionic effects may result from a depressant action on nerve fibers. The site or sites of action have not been localized but it is known that the barbiturates interfere with those reflexes involved in the compensatory mechanisms brought into play by changes in position. The hypotensive response elicited by the subcutaneous administration of methacholine (Funkenstein test) is enhanced by the prior administration of amobarbital.[15] The similarity in the quantitative response of diastolic blood pressure in hypertensive patients to both secobarbital and tetraethylammonium bromide also suggests that the barbiturates affect autonomic mechanisms,[16] but it is unlikely that they act at the same level of the reflex arc as does tetraethylammonium. Barbiturates also are capable of exerting effects at the skeletal myoneural junction but these actions are of little significance at the levels of dosage used therapeutically.

Other effects—There is little evidence that hypnotic or sedative doses of barbiturates directly affect the gastrointestinal tract to a significant degree. Any beneficial effects they may have on symptoms of gastrointestinal diseases are very likely secondary to depression of the central nervous system. In laboratory animals varying effects have been noted on gastrointestinal tone, motility and secretions, but only with doses in excess of those usually used to produce sleep or sedation in man.

Anesthetic doses of the barbiturates are

capable of affecting certain renal functions in dogs, particularly renal tubular functions, but there is no evidence that they have a direct action on the kidneys at the hypnotic or sedative dose level in man.

The uterus is quite resistant to the smooth muscle-depressant effect of the barbiturates, but barbiturate anesthesia will prolong labor as a consequence of impairment of force and frequency of uterine contraction.

Although barbiturates in therapeutic doses do not affect hepatic function, jaundice may occur with acutely toxic amounts and there is some evidence that these drugs may aggravate pre-existing liver disease.

Alterations in the fluid portion of the blood as well as the formed elements have been described in various laboratory species, but ordinary therapeutic doses of barbiturates have little if any effect on the blood constituents in man. Small soporific doses do not significantly alter the basal metabolic rate but may lower body temperature slightly. Larger doses can decrease body temperature markedly, even in the absence of any great alteration in basal metabolic rate.

Other metabolic effects of the barbiturates have been described in laboratory animals but their possible significance in man is not clear. Hyperglycemia occurs occasionally during barbiturate anesthesia but this is variable and depends on a number of factors—the particular barbiturate employed, the dose, and the route of administration. Similarly, consistent alterations in cerebrospinal fluid pressure have not been seen during barbiturate anesthesia.

Physiologic Disposition of Barbiturates

Absorption of barbiturates from the gastrointestinal tract is adequate, the rectal route being more efficient than is oral administration. Longer-acting compounds generally are absorbed more slowly than are those with shorter durations of action, and the absorption rate is much more rapid when the parenteral route is employed. After oral administration the time required for blood concentrations to attain maximal values roughly parallels the duration of action of the compound used. Phenobarbital, which has a long duration of action, may not appear in the blood in maximal amounts until 12 to 18 hours after its ingestion.[17]

Equilibrium between the concentrations in blood and most body tissues and fluids occurs rapidly. Inasmuch as the different barbiturates are bound in varying degrees to plasma albumin, this will determine the fraction of a dose that is available for diffusion into other fluids and tissues. A fair degree of correlation exists between the degree of depression of the central nervous system and the blood level of drug when the ultrashort-acting and short-acting barbiturates are given, but this is not true with the long-acting compounds. Evidence indicates that the barbiturate compounds enter all cells and their binding to proteins within the cells follows the same order as that occurring in blood, pentobarbital and secobarbital being bound to the greatest extent, phenobarbital to a lesser degree, and barbital the least.

Of the barbiturates studied thus far, with the exception of hexobarbital and the thiobarbiturates, uniform distribution throughout tissues appears to be the rule. Concentrations are somewhat higher in the liver and kidneys than in other tissues, attributable perhaps to a greater degree of protein binding in these structures. Hexobarbital and the thiobarbiturates pass from other tissues and fluids into fat, where higher concentrations are attained. This selective distribution to adipose tissue apparently is of major importance in limiting the duration of action of these compounds, inasmuch as their rates of metabolism in man are not significantly different from those of some of the intermediate-acting and longer-acting compounds.

Concentrations of the barbiturates in the brain are not significantly different from those in the blood, but equilibrium between these two sites is established more slowly with some compounds than with others. There is a dearth of information on the distribution between cerebrospinal fluid and plasma. The most reliable data from studies in man place these ratios (cerebrospinal fluid to plasma) below 1, and between 0.4 and 0.6 for phenobarbital.

Metabolic alteration of the barbiturates oc-

curs predominantly in the liver. The kidneys play a lesser role, and other tissues appear to contribute little in the chemical alteration of these compounds in vivo. The types of metabolic alteration they may undergo are as follows: (1) oxidation of side chains in the 5 position with the formation of keto, hydroxy and carboxy derivatives; (2) loss of alkyl substituents on the nitrogen atom in compounds in which such substitutions occur; (3) desulfuration of thiobarbiturates, and (4) hydrolytic opening of the barbituric acid nucleus. Reviews by Maynert and van Dyke,[18] Maynert,[19] Brodie,[20] and Richards and Taylor[21] contain more detailed accounts of the metabolic disposition of the barbiturates.

The enzyme systems responsible for some of these metabolic alterations have been localized within the cell and many of their characteristics determined.[21] The major portion of the barbiturates and their metabolites are eliminated from the body by the renal route. Those that are excreted in appreciable quantities in unaltered form exhibit cumulative action with repeated administration, and in the presence of impaired renal function prolongation of action and even severe poisoning may occur. Barbital is one such compound; a single dose may require as long as 8 to 12 days for complete excretion. The renal clearance rates of other barbiturates that have been studied are extremely low;[17] the values for barbital, phenobarbital and aprobarbital are much less than the rate at which glomerular filtrate is formed.

Barbiturate Tolerance and Idiosyncrasy

Prolonged administration of pentobarbital, secobarbital or amobarbital results in a limited degree of tolerance in man,[22] and Gruber and Keyser[23] have demonstrated tolerance to the depressant effects of several barbiturates in various laboratory animals. Partial cross tolerance between different barbiturates has been demonstrated, and when the drug is discontinued a rapid loss of tolerance occurs.

Therapeutic doses of barbiturates may induce a number of abnormal responses, ascribed to either an inherent or an acquired sensitivity. Manifestations of inherent sensitivity usually appear as an aberration or exaggeration of the normal response of the central nervous system. A neurotic person not uncommonly exhibits the so-called hang-over for an unusually long period after other evidence of barbiturate action has disappeared. Under this heading one might also include headache, nausea, emotional disturbances, vomiting and diarrhea. An instance of unusual sensitivity of the respiratory center to the depressant effect of a thiobarbiturate[24] perhaps could also be ascribed to inherent or natural sensitivity. Allergylike reactions, on the other hand, are considered the result of an acquired sensitivity, and hence they occur only infrequently after a single dose of a barbiturate. Skin eruptions, a variety of which have been described, are the most common manifestations of this type of idiosyncrasy.

Enhancement of Barbiturate Action

A number of substances enhance the depressant effects of barbiturates. In many instances it is not clear whether the observed effects are the result of simple summation or of potentiation. Administration of an appropriate agent with a barbiturate may either prolong the duration of action of the latter or increase the depression produced. Some substances (e.g., calcium salts, acetylcholine, tetraethylthiuram disulfide, certain surface-active agents, mephenesin, several intermediary metabolites) may even restore anesthesia in animals subsequent to awakening from an anesthetic dose of a barbiturate. Richards and Taylor[21] have suggested that a reduction in the rate of metabolic alteration or excretion of the barbiturate, an increased sensitivity of the central nervous system to its depressant effects, and an alteration in its distribution in the body may be possible mechanisms in the production of such effects.

Acute Barbiturate Toxicity

It is difficult to state with any degree of certainty the incidence of acute poisoning by the barbiturates, but it has been estimated that one of every 2000 hospital admissions is for

acute intoxication by one of these drugs. Self-medication is undoubtedly the most common cause of acute poisoning, and intended suicide probably accounts for the majority of cases. In a few, unintentional poisoning may be the result of "automatism."[25] On occasion, poisoning may be due to an inadvertent overdosage by the physician. This is most likely to occur when an inadequately informed or inexperienced person administers the drug intravenously. A relatively rare cause of intoxication is idiosyncrasy.

Acute barbiturate intoxication usually can be diagnosed on the basis of the history, the signs and symptoms, and chemical analysis of excreta, gastric contents or body fluids. Depression of the central nervous and cardiovascular systems accounts for most of the physical findings. Respiratory depression, one of the outstanding manifestations, usually occurs early, but it may be delayed, particularly when the newer preparations having delayed actions are involved. In one reported case there was no evidence of depression during the first nine and one-half hours after ingestion of the barbiturate, yet coma supervened four and one-half hours later.[26]

The use of certain therapeutic measures, particularly analeptics, should be based on the degree of depression. Not uncommonly, these pharmacologic antagonists are used in situations where they are not indicated and, unfortunately, at times to the exclusion of certain symptomatic forms of treatment that might have been more effective. This lack of discretion in the employment of such agents undoubtedly has been a factor in causing some physicians to deprecate the effectiveness of certain drugs as respiratory stimulants.

Careful and repeated determinations of blood pressure, pulse, respiration and reflexes are helpful in assessing the degree of depression and the effectiveness of therapy. The pentylenetetrazol test (intravenous injection of 5 cc. of a 10 per cent solution) may help determine the depth of coma. Should previously absent reflexes return or purposeful movements ensue, the use of a pharmacologic stimulant is not indicated.

A number of central stimulants have been employed for treatment of acute barbiturate intoxication. A careful survey of the literature by Fazekas and Koppanyi[27] led them to conclude that pentylenetetrazol and picrotoxin are the most effective. Both drugs should be given intravenously, the former in a dose of 500 mg. every 10 or 20 minutes until consciousness or reflexes return. Various dosage schedules of picrotoxin have been followed. One calls for administering 6 mg. and then increasing the doses by 3 mg. at 15 minute intervals until a 15 mg. dose is reached, after which the dosage is regulated on the basis of the patient's response. The drug usually is given until some purposeful movement is made.

Recently two new central nervous system stimulants, bemegride and aminophenazole, have been recommended for treatment of barbiturate poisoning. It has not been possible to determine whether these compounds are better than picrotoxin and pentylenetetrazol.

The most important aim of symptomatic therapy is the maintenance of an adequate respiratory exchange. Whether or not analeptics are employed, a free airway is essential and artificial respiration is indicated in situations where respiration has ceased but cardiac function is maintained. Medullary stimulation has been realized by electric rather than chemical means, but such procedures do not appear to offer any benefits not obtainable from artificial respiration or judicious use of appropriate chemical agents. Effective medullary stimulation will result in improvement of cardiac and circulatory function by enhancing central vasomotor tone and reducing anoxia. Gastric lavage, catharsis and diuresis are aimed at enhancing removal of barbiturate from the body. The lavage will remove unabsorbed barbiturate from the stomach and provide material for diagnostic toxicologic examination. Administration of magnesium sulfate in a dose of 15 to 30 gm. in warm water by lavage tube serves to increase the rate of passage of any unabsorbed drug along the gastrointestinal tract. Catheterization in the presence of coma and maintenance of an adequate urinary flow are essential, since the kidneys represent the main channel of excretion of the barbiturates and their metabolites. The effec-

tiveness of the artificial kidney in removing barbiturates from the blood has been established,[28] but the practicability of this method for routine treatment of barbiturate intoxication is doubtful. The usual measures to combat shock should be taken if it occurs, and administration of salt-poor albumin may be effective in alleviating cerebral edema.[29] Careful attention to bronchial secretions and changing the position of the patient are helpful in preventing hypostatic pneumonia. One can minimize the danger of pulmonary infection by administering one of the broad-spectrum antibiotics prophylactically.

The mortality rate for acute barbiturate intoxication in this country is estimated as somewhat less than 10 per cent. A number of factors can influence the prognosis, namely, the compound ingested, dose, the duration of poisoning, physical condition of the patient, and the therapy employed.

Chronic Barbiturate Toxicity

Available information indicates that chronic intoxication with the barbiturates is much more common at present than is narcotic addiction. Some psychic deviation appears to be essential in determining whether or not introduction to a barbituric agent will lead to chronic use. Psychoneurotic persons initially employ the barbiturates for their hypnotic effect, whereas it is believed that psychopathic persons use them from the start to induce intoxication rather than sleep. Prolonged use of these drugs can lead to true addiction.

During the period of chronic intoxication the signs and symptoms resemble those of chronic alcoholism: impairment of mental ability, confusion, regression, increased emotional instability, nystagmus, dysarthria, ataxia, and depression of superficial and abdominal reflexes. Although abnormal electroencephalographic changes appear and persist during the course of intoxication, a certain degree of tolerance develops to the clinical effects of these agents.[30]

During the first 12 to 16 hours after abrupt withdrawal of the drug, the signs of intoxication disappear. Also during this time, other signs and symptoms appear, e.g., anorexia, nausea and vomiting, rapid weight loss, fever, and evidences of increased irritability of the central nervous system. From the sixteenth hour up to the fifth day after withdrawal, convulsions of the grand mal type may occur and the development of a psychosis is not uncommon. Symptoms usually disappear over two to three weeks, and recovery is usually complete. However, death has followed the abrupt withdrawal of barbiturates.

Treatment of barbiturate intoxication requires hospitalization. Abrupt withdrawal or rapid reduction in dosage is extremely hazardous and not to be employed. After establishing the dose necessary to maintain a state of mild intoxication, dosage is reduced, the rate determined by the response of the patient. If any evidence of abstinence appears, further reduction of dosage should be terminated temporarily. Close observation of the patient is necessary during withdrawal, with particular attention to maintenance of fluid and electrolyte balance. When withdrawal is complete, psychotherapy and rehabilitative measures should be instituted.

Nonbarbiturate Hypnotics; Bromides

Potassium bromide was first employed as a hypnotic in 1864 by Behrend. Since then a number of inorganic salts of bromine have found therapeutic application. Of these, only sodium and potassium bromides are extensively used at present. The synonyms or proprietary names and hypnotic doses of the official and N.N.D. hypnotics and sedatives not containing the barbituric acid nucleus are listed in table 2.

Actions of Bromides

Although the bromides are capable of affecting other organs and organ systems when toxic concentrations occur in the body, the only significant effect realized with therapeutic doses is depression of the central nervous system. Administration usually is controlled so that only sedation results. When large doses are given over a prolonged period, marked depression and even coma may ensue. At a proper dose level the sedative action of this

TABLE 2

OFFICIAL AND N.N.D. NONBARBITURATE HYPNOTICS AND SEDATIVES

DRUG	SYNONYMS OR PROPRIETARY NAMES	AVERAGE ORAL HYPNOTIC DOSE FOR ADULTS (GRAMS OR CUBIC CENTIMETERS)
Bromides* U.S.P., N.F.		1.0†
Chloral hydrate U.S.P.		0.5-2.0
Petrichloral N.N.D.	Pentaerythritol chloral; PERICLOR®	0.6
Paraldehyde U.S.P.		3.0-8.0
Ethchlorvynol N.N.D.	PLACIDYL®	0.5
Ethinamate N.N.D.	VALMID®	0.5
Methyprylon N.N.D.	NOLUDAR®	0.2-0.4
Glutethimide N.N.D.	DORIDEN®	0.5-1.0
Carbromal N.F.	URADAL®, ADALIN®, PLANADALIN®, BROMADAL®, NYCTAL®	0.6-1.3
Bromisovalum N.F.	BROMURAL®, BROMISOVAL®, UVALERAL®, BROVALUREA®, DORMIGENE®	0.6
Ectylurea N.N.D.	NOSTYN®	‡

*Usually employed as the sodium or potassium salt. Calcium, lithium and strontium salts are available but possess no advantages.

†It is recommended that this dose be given three times per day, but dosage usually must be adjusted for each patient to obtain the desired effect.

‡Recommended only as a sedative to be employed in doses of 0.15 to 0.3 gm. three to four times per day.

ion is realized, and under appropriate environmental conditions drowsiness and sleep result. Bromide-induced sleep is not necessarily the most restful; it is commonly filled with more dreams than normal, and hang-over is not infrequent. More marked depression occurs with larger doses than those resulting in sedation and is associated with signs and symptoms characteristic of chronic bromide intoxication or bromism.

The effectiveness of bromides in treatment of epilepsy has been known for some time, and Merritt and Putnam[31] in 1938 demonstrated the capacity of these compounds to depress the motor cortex. The associated suppression of activity in other areas of the cerebral cortex makes them somewhat less desirable in the treatment of epilepsy than certain newer agents (e.g., diphenylhydantoin) which elevate the convulsive threshold of the motor cortex without significantly altering other functions of the central nervous system.

The mechanism or mechanisms by which the bromide ion suppresses activity in the central nervous system are not entirely clear. Early experiments in which various organs were perfused with solutions wherein the chloride ion was replaced by the bromide ion led to the conclusion that only the central nervous system is affected by the presence of the bromide ion in the extracellular medium. However, it has been shown more recently that the contractile characteristics of muscle may be significantly affected by the presence of bromide ion in the surrounding fluid.[32,33] It also has been generally assumed that the depressant effects of the bromide ion are due entirely to its presence in the extracellular fluid and that the cells of the central nervous system are relatively impermeable to this ion. More recent experiments[34] in which radioactive bromide (administered as NH_4Br^{82}) was employed suggest that the labeled material gained access to cells in the central nervous system. Should this prove to be true, it may be necessary to seek a site of action at the intracellular level.

Physiologic Disposition of Bromides

Bromides, like chlorides, are absorbed rapidly from the gastrointestinal tract. Although

chlorides do not seem to interfere with absorption of bromides, evidence suggests that the bromide ion may interfere with absorption of chlorides. Distribution of the bromide ion in the body is similar to that of the chloride ion, and except for the red blood cells and perhaps the cells of the central nervous system bromides do not pass the cell membrane. The bromide ion may replace more than its equivalent of chloride in the erythrocyte,[35] since the ratio of bromide in cell water to bromide in plasma water lies between 0.8 and 0.9. The bromide-to-chloride ratio in the extracellular fluid is similar to that in plasma, but even after intravenous administration the equilibrium between cerebrospinal fluid and plasma is not attained for 24 hours, when the concentration in the plasma is two and one-half to three times that in the cerebrospinal fluid.

After administration of bromides there is no increase in the total halogen ion content of the extracellular compartment. As the bromide concentration increases, chloride ion concentration decreases proportionately so that the concentration of halides is maintained at approximately 100 mEq. It then follows that the ratio of concentration of the two ions will be established by the ratio in the diet. Maintenance of a constant proportion of bromide to chloride in the diet causes the concentration of serum bromide to rise until it approaches an equilibrium value where the percentage of bromide in serum halide to that in dietary halide is greater than one suggesting preferential excretion of chloride. This is borne out by the experiments of Wolf and Eadie,[36] who found that renal excretion of bromide proceeds at a slower rate than does excretion of chloride.

Bromide excretion can be enhanced by administration of chloride or by use of a mercurial or xanthine diuretic. Up to one-fifth the daily intake may appear in the feces when bromides are administered over a long period. Other body secretions (tears, sweat, bile, milk, saliva, gastric juice) will contain small amounts of bromide following the ingestion of bromide preparations, and hydrobromic acid will appear in the gastric juice, the gastric mucosa employing the bromide in the extracellular fluid to form hydrobromic acid.[37, 38] The bromide ion finds its way across the placenta and is present in the urine of newborn infants whose mothers have received bromide preparations.

Toxicity of Bromides

Acute bromide poisoning is almost unheard of, since oral doses of sufficient magnitude to result in manifestations of toxicity are so large that they produce gastric irritation and vomiting. Chronic bromide intoxication or bromism is not rare at present in spite of the popularity of the tranquilizers. There are a variety of preparations available for self-medication, and prescription of bromide-containing sedatives by physicians is not uncommon.

Symptoms of intoxication can develop rapidly or slowly. Alterations in the function of the central nervous system are the most common. The psychic changes (drowsiness, disorientation, loss of memory for recent events, confabulation, delirium, hallucinations, headache, weakness) generally occur prior to the appearance of neurologic changes. The latter include lessening of sensory perception, slowness and thickness of speech, ataxia, tremors, vasomotor disturbances and incoordination. Reflexes may be increased but usually are decreased or absent. Ocular disturbances may occur and appear early, and occasionally nystagmus and photophobia are seen. In place of the regular rhythm of the normal electroencephalogram there may appear irregular, slow, 3 to 7 per second waves in all leads.[39] A bromide psychosis and the associated signs of bromism simulate a number of disorders and can be recognized only by chemical analysis of blood for bromides.

Chronic administration of bromides commonly affects the skin and gastrointestinal tract. An acneiform rash is seen in about 20 per cent of cases. There may be rather extensive involvement of the skin without any evidence of depression of the central nervous system, or vice versa. Although the previously named type of dermatitis is most common, other and more bizarre forms may occur. Pemphiguslike, pustular and ulcerative lesions as well as a nodular-type lesion (nodose bro-

moderma) have been described. There does not appear to be a direct correlation between the level of bromide in the blood and the changes seen in the skin. Adverse effects on the gastrointestinal tract include dryness of the mucous membranes, anorexia, fetid breath, impaired digestion and even emaciation. Constipation and other gastrointestinal symptoms may appear, and inadequacy of fluid intake may give rise to dehydration and low grade fever. Adverse effects on the respiratory and reproductive systems have been described.

It is not possible to establish a precise correlation between blood levels and severity of intoxication, but there are evidences of confusion when concentrations in serum are between 50 and 150 mg. per 100 cc. Levels above 150 and up to 200 mg. per 100 cc. appear to be necessary to result in neurologic changes. Above 200 mg. per 100 cc., toxic psychoses usually result, and when levels over 300 mg. per 100 cc. are reached life is in jeopardy.

In treatment of chronic bromide intoxication every effort should be made to enhance elimination of the ion. Measures include administration of sodium chloride (4 to 8 gm. per day along with 1 to 2 l. of parenterally administered physiologic saline), interrupted administration of ammonium chloride (6 gm. per day in divided doses), mercurial diuretics (every second or third day), and maintenance of a high fluid intake (minimum of 4 l. per day). Treatment of the other manifestations of poisoning is symptomatic. Following recovery from intoxication one should attempt to correct the underlying factors that caused the patient to seek refuge in the drug.

Chloral Hydrate; Actions

The effects of chloral hydrate and a derivative, petrichloral, appear to be qualitatively similar. It has been claimed that the latter compound is less likely to produce certain adverse gastrointestinal symptoms than the former. Hypnotic doses of chloral hydrate usually produce drowsiness in 10 to 15 minutes and sleep within an hour. Duration of action is in the neighborhood of five hours, and little hang-over is evident on awakening. Reflexes are not impaired significantly, and for this reason the drug is not of great value as an anticonvulsant. Larger doses induce progressively greater degrees of depression, and if they are of sufficient magnitude general anesthesia will result. The anesthetic state is characterized by rather marked depression of the vasomotor and respiratory centers. Recent evidence[40] indicates that the depressant potency of trichloroethanol, a metabolic product of chloral hydrate, is not significantly different from that of the parent compound, and there is reason to believe that this metabolite may account for the effects on the central nervous system which in the past have been attributed to chloral hydrate.

In therapeutic dosage chloral hydrate may produce slight hypotension as a result of mild central vasomotor depression and muscular relaxation. There is on record one instance of marked abnormality in cardiac rhythm after ingestion of 12 gm. chloral hydrate,[41] but the effects of this hypnotic agent on the cardiovascular system usually are not significant. Although renal and gastrointestinal effects have been noted, they usually are of no great magnitude and are quite variable. Inflammatory changes can be produced by application of chloral hydrate to the skin, and the nausea and vomiting which have occurred after ingestion of poorly diluted solutions of the drug have been ascribed to its irritant action. A number of cutaneous reactions have been observed following ingestion of the drug[42] and sensitivity appears to be the predominant factor in their occurrence.

Physiologic Disposition of Chloral Hydrate

Adequate and fairly rapid absorption of chloral hydrate takes place from all mucous membrane-covered surfaces. Little is known about the distribution of this compound in the body. Trichloroacetic acid, trichloroethanol and urochloralic acid (the glucuronide of trichloroethanol) are the major biotransformation products of chloral hydrate and are found in the urine following administration of this drug. The fraction of a dose found in the urine appears to bear little relationship to the amount administered. Marked individual var-

iation is noted as well as variation from day to day in the same person. Whereas it appears that only the liver and kidneys are able to convert chloral hydrate to trichloroacetic acid,[43] most tissues seem to participate in the reduction of the drug to trichloroethanol. Failure to detect significant concentrations of chloral hydrate in the blood following its administration has been used as an argument to explain the activity of chloral hydrate on the basis of its metabolism to trichloroethanol, which appears to have the same hypnotic activity in man as does the parent compound.[40] Since urochloralic acid possesses reducing properties, its presence in the urine can give rise to a positive test with reduced alkaline copper reagents such as Fehling's solution and Benedict's solution.

Toxicity of Chloral Hydrate

Manifestations of acute intoxication with chloral hydrate are similar to those of acute intoxication with other depressants of the central nervous system. Vomiting may occur as a result of its irritant effects on the stomach. It is difficult to state with any degree of certainty the lethal dose, but the average is approximately 10 gm.; death has occurred following ingestion of 1 to 3 gm. and recovery has followed administration of 30 gm. Marked depression with coma, dyspnea or very slow respiration, cyanosis and hypotension occur rapidly and death usually is not delayed longer than five hours. Hepatic damage with jaundice and albuminuria as a consequence of renal irritation have been reported in persons who have recovered from acute intoxication with chloral hydrate. Treatment consists of gastric lavage and the use of appropriate measures to maintain respiration and blood pressure. Supportive therapy of the type employed in acute barbiturate intoxication is indicated.

Chronic use of chloral hydrate or the "chloral habit" is not common. The picture is similar to that of chronic alcoholism, with manifestations of gastric irritation and cutaneous alterations being more marked. Continued use of chloral hydrate will produce psychic dependence and slight tolerance to the depressant effects of the compound. Therapy of chronic intoxication involves withdrawal of the drug and subsequent psychiatric rehabilitation. A state resembling delirium tremens may occur and is treated in essentially the same manner as the similar condition seen in chronic alcoholism.

Paraldehyde

This compound, a polymer of acetaldehyde, is a safe and effective hypnotic, but its unpleasant odor and taste have limited its therapeutic usefulness. In the presence of air and sunlight, oxidation to acetic acid occurs.[44] Storage in airtight amber bottles minimizes this deteriorative change but caution should be exercised in using old preparations.

Actions of Paraldehyde

Paraldehyde is more potent than alcohol and acts more rapidly, but the effects of the two substances on the central nervous system are qualitatively similar. Sleep usually is induced in 10 to 15 minutes and persists for four to eight hours. Adverse cardiac effects, acute right-sided heart-failure and cardiac dilatation, have been reported after administration of lethal doses of paraldehyde. However, when therapeutic doses are employed there are no significant alterations in tissues or organs other than the central nervous system.

Physiologic Disposition of Paraldehyde

Rapid absorption of paraldehyde occurs following either oral or parenteral administration and the characteristic odor is detectable on the breath shortly after ingestion. It appears that the drug is widely distributed in all tissues and passes the placental and blood-brain barriers. Concentrations in the brain are somewhat higher than those in blood.[45] Although our knowledge of the elimination and metabolism of paraldehyde in man is somewhat meager, it would appear that a fraction is eliminated unchanged by way of the lungs and a very small amount is excreted in the urine. The major portion is completely metabolized to carbon dioxide and water, apparently after depolymerization to acetic acid. Administration of hepatotoxic agents to ani-

mals prolongs the action of paraldehyde, and the liver undoubtedly plays a major role in metabolism of the drug.

Paraldehyde Toxicity

Acute intoxication with paraldehyde is relatively rare, since a number of other agents with less objectionable tastes and odors are available. Individual susceptibility to the depressant effects of paraldehyde seems to vary considerably, but in general the toxicity is low and the margin of safety of the drug is extremely wide. As little as 12 cc. administered rectally has produced death, and survival has been reported following the oral ingestion of as much as 120 cc. Blood levels ranging from 54 to 148 mg. per cent have been reported in persons who died as the result of ingestion of paraldehyde.[45] Manifestations of poisoning are for the most part referable to the central nervous system; treatment is little different from that employed in chloral hydrate poisoning. Decomposed paraldehyde, containing high concentrations of acetic acid, is extremely irritating and may produce necrosis of any tissue it contacts.[44]

The very rare case of chronic paraldehyde intoxication exhibits many of the features of chronic alcoholism and is treated similarly. Chronic use of the drug will result in some degree of tolerance and in habituation. Although it has been claimed that addiction to paraldehyde can occur, this is very doubtful.

Tertiary Carbinols and Derivatives

The capacity of tertiary carbinols to depress the central nervous system has been generally recognized in pharmacology for some time, but only recently have compounds of this type found widespread application. Among the first employed as a hypnotic was amylene hydrate, whose only use at present is as a solvent. More recently a large number of tertiary carbinols and their derivatives have been synthesized and evaluated for hypnotic and other pharmacologic activity. From this group have emerged three compounds (methylparafynol or DORMISON®, ethchlorvynol and ethinamate) which appear to have sufficient promise to be applied practically. Methylparafynol is not official, nor is it listed in N.N.D.

Ethchlorvynol—Ethchlorvynol (ethyl β-chlorovinyl ethynyl carbinol, Placidyl), a colorless liquid, appears to possess approximately the same potency and toxicity as phenobarbital. In man its hypnotic action is mild and less pronounced than that obtained with the barbiturates, and hang-over is less frequent. In hypnotic doses its duration of action is approximately five hours and it does not affect other organs and organ systems significantly. In addition to hypnotic activity the drug exhibits anticonvulsant properties. Following oral administration, absorption from the gastrointestinal tract is rapid and the major portion of the drug appears to be metabolized, the liver playing a predominant role. The features of acute and chronic intoxication with this drug in man remain to be established. Present evidence suggests that side effects are fewer and less marked than those associated with use of barbiturates.

Ethinamate—Ethinamate (Valmid) is 1-ethynylcyclohexyl carbamate and occurs as a crystalline powder. Comparative studies in laboratory animals have shown that it possesses approximately the same therapeutic index as secobarbital and about one-half the duration of action. Its effects on the central nervous system in man are qualitatively similar to those of the barbiturates and it is approximately one-fifth as potent as but more rapidly acting than secobarbital.[46] Administration of a hypnotic dose at bedtime results in few or no aftereffects and does not alter respiration, blood pressure or pulse significantly. Ethinamate, like ethchlorvynol, has anticonvulsant properties as well as a weak local anesthetic action, but significant effects on other organs or systems after therapeutic doses have not been demonstrated. Ethinamate is adequately absorbed from the gastrointestinal tract. Evidence suggests that the liver and a number of other tissues participate in its metabolism, only small amounts of unchanged drug appearing in the urine. Abnormal hepatic function or renal disease does not seem to enhance or prolong its action.

Several cases of acute intoxication with

ethinamate have been reported in the German literature and two deaths have been associated with its ingestion, but there has been no instance in which a fatality could be attributed solely to ethinamate administration. A careful and reliable description of the signs and symptoms of acute poisoning with ethinamate is not available, but it would appear that the manifestations are similar to those following an overdose of a short-acting barbiturate and treatment should proceed along lines similar to those utilized when poisoning is caused by the latter. Ethinamate has not been in use long enough to obtain any information concerning its chronic toxicity for man.

Piperidinediones

Methyprylon—Methyprylon (3,3-diethyl-5-methyl-2,4-piperidinedione, Noludar) resembles pentobarbital and secobarbital in its effects on the central nervous system. Somewhat less potent than the latter barbiturate, hypnotic doses produce sleep in 10 to 30 minutes and the action usually persists for approximately six hours.[47] Although it possesses anticonvulsant and antiemetic properties, their clinical application is unlikely since other more effective compounds are available. Electroencephalographic changes in laboratory animals are similar to those produced by pentobarbital. Significant alterations in the cardiovascular system have not been observed following hypnotic doses of methyprylon, but prolonged hypotension has occurred in one case of fatal poisoning.[48] Other than occasional nausea and vomiting, adverse effects have not been described following therapeutic doses. Methyprylon is adequately absorbed from the gastrointestinal tract and maximal plasma concentrations are attained in one to two hours.[49] Small amounts of the drug are excreted unchanged in the urine, with about equal amounts appearing as a dehydrogenated derivative.

On occasion, vertigo, nausea, vomiting and syncope have been noted after hypnotic doses of methyprylon. The lethal dose has not been established but death has followed ingestion of 6 gm. and survival has occurred after 9 gm. In the former case[48] respiration was somewhat diminished in the early phase of poisoning, but the most striking feature was persistent hypotension which responded only to the continuous administration of norepinephrine. Postmortem examination following death on the fifth day revealed changes similar to those appearing after a prolonged hypotensive period. In treating acute methyprylon poisoning, it appears that one should direct attention to the respiratory and vascular changes. Pentylenetetrazol, picrotoxin and strychnine reportedly are effective in counteracting the respiratory depression, and the beneficial effects of norepinephrine in one case of poisoning would recommend this agent for treatment of the hypotension. Additional therapy should consist of those supportive and symptomatic measures employed in treatment of poisoning by other depressants of the central nervous system such as the barbiturates. Methyprylon has not been in use long enough to assess the potential hazards of its chronic administration.

Glutethimide—Glutethimide (2-ethyl-2-phenylglutarimide; 3-ethyl-3-phenyl-2,6-piperidinedione; Doriden) was synthesized in 1952 and is chemically similar to methyprylon. Its hypnotic potency appears to be approximately one-fifth that of secobarbital.[50] Sleep ordinarily occurs one-half to one hour after ingestion of a hypnotic dose and persists uninterrupted for from four to eight or 10 hours. In doses below 750 mg. the drug infrequently produces hangover. Larger doses depress the central nervous system to a more severe degree, and with sufficiently large amounts unconsciousness ensues, reflexes are diminished or absent, the pupils dilate, and hypothermia develops. The respiratory depression produced by glutethimide, like that resulting from methyprylon, is not as marked as that seen in barbiturate intoxication.[51] The electroencephalographic pattern is similar to that observed after barbiturates.[50] Significant alterations in the cardiovascular system have not occurred with hypnotic doses, but hypotension is rather common when overdoses of the drug are taken.

Little information is available on the physiologic disposition of glutethimide. The rate at which effects appear in man following oral ingestion indicates that absorption from the gastrointestinal tract is adequate and fairly

TABLE 3

INDICATIONS FOR USE OF HYPNOTIC AND SEDATIVE AGENTS

BARBITURATES

1. Sedation
   Emotional crises associated with anxiety tension states of a temporary nature, hypertension, hyperthyroidism, nausea or vomiting of nonorganic origin, infantile pylorospasm, maniacal conditions, delirium tremens, etc.; to counteract undesirable stimulation of central nervous system caused by certain sympathomimetics; intravenously to combat fear or hysteria in cases of severe burns.
2. Hypnosis
   Temporary relief of nervous insomnia.
3. Anesthesia
   General anesthesia (ultrashort-acting agents intravenously), basal anesthesia (oral or rectal administration), preanesthetic medication.
4. Potentiation of analgesia
   When combined with salicylates, or derivatives of p-aminophenol or pyrazolone.
5. Anticonvulsant action
   Treatment of convulsant poisoning and convulsions of other origin (tetanic spasms associated with tetanus, eclampsia, cerebral hemorrhage, status epilepticus, etc.); symptomatic therapy of epilepsy (phenobarbital, metharbital, mephobarbital).
6. Psychiatric uses
   Narcoanalysis; prolonged hypnosis for treatment of psychic casualties; in electroencephalography to bring out abnormalities and obtain satisfactory records in infants and children.

NONBARBITURATES

1. Sedation
   Temporary relief of simple anxiety and nervous tension (bromides, ectylurea and perhaps other compounds); treatment of chronic bromide poisoning when sedation is required (paraldehyde).
2. Hypnosis
   Withdrawal phase of opiate addiction and chronic alcoholism (chloral hydrate); to combat fear and exhaustion in cases of severe burns; delirium tremens (paraldehyde); temporary relief of simple insomnia (all agents except bromides and monoureides).
3. Anesthesia
   Preanesthetic medication (ethinamate and perhaps others).
4. Anticonvulsant action
   Symptomatic therapy of epilepsy (bromides).

rapid. Data from animal experiments suggest that there is a wide distribution of the compound or its metabolites or both. A large amount of the material, after undergoing some metabolic transformation, finds its way into the gastrointestinal tract via the bile. When radioactively labeled glutethimide is administered to animals, approximately one-third of the activity appears in the urine within 15 to 16 hours. Practically all of the drug excreted by this channel is chemically altered and is of unknown structure.

Untoward effects following hypnotic doses of glutethimide are infrequent. Skin rashes and nausea have been reported but hang-over is not common. Several cases of intoxication have occurred and six deaths have been ascribed to ingestion of glutethimide. The lethal dose for man seems to be between 10 and 20 gm.[52] although survival has followed ingestion of as much as 15 gm.[51] In four of the six reported fatalities the nature of the agent involved was established by toxicologic analysis. The manifestations of poisoning in most instances are similar to those in intoxication with other hypnotic agents. Although a number of analeptics have been employed to combat the respiratory depression (picrotoxin, caffeine, amphetamine, etc.), it appears that the most favorable results have been obtained with picrotoxin. If respiratory arrest occurs, artificial respiration should be employed, and administration of a vasoconstrictor such as phenylephrine or mephentermine has been successful in combating the hypotension which may sometimes develop. Other treatment is of a supportive or symptomatic nature, as in acute barbiturate intoxication. Recovery from poisoning should be followed by psychiatric rehabilitation. As yet, severe adverse reactions have not appeared during the chronic use of glutethimide, but it is likely that manifestations of chronic toxicity will be seen with longer and more widespread use of the drug.

Monoureides

Monoureides are chemically similar to barbiturates in that they are derivatives of urea, but unlike the barbituric acids one of the amino groups has not been condensed with a carboxyl group. A number of such compounds have been synthesized in the past and have received clinical trial, among them carbromal and bromisovalum. Although both drugs still are included in the "National Formulary," the results that have been obtained with them are anything but promising due to their feeble

TABLE 4

CONTRAINDICATIONS TO USE OF SEDATIVE AND HYPNOTIC DRUGS

1. Certain psychiatric states
   Particularly psychoneuroses or constitutional psychopathic states (prolonged use of any one of these drugs, particularly the barbiturates); undiagnosed nervous or mental disorders (bromides).
2. Hepatic dysfunction
   Shorter-acting barbiturates, chloral hydrate, paraldehyde.
3. Renal dysfunction
   Long-acting barbiturates, bromides, chloral hydrate.
4. Idiosyncrasy
   Should be considered before administering any sedative-hypnotic drug.
5. Conditions in which any respiratory depression is contraindicated
   Barbiturates.
6. Addison's disease, hyperthyroidism, diabetes mellitus
   Barbiturates poorly tolerated.
7. Malnutrition and dehydration
   Bromides.
8. Dermatitis
   Bromides.
9. Inflammation of gastrointestinal tract
   Chloral hydrate, paraldehyde.
10. Cardiac disease
    Chloral hydrate.
11. Bronchopulmonary disease
    Paraldehyde.

depressant effects. More recently a nonbromide-containing monoureide has been prepared and employed as a sedative for relief of mild tension. This compound, ectylurea (2-ethyl-*cis*-crotonylurea, Nostyn), produces a mild depression of the central nervous system and appears to have a rather wide sedative dose range. The usual therapeutic doses do not significantly affect other body systems. The drug is well absorbed from the gastrointestinal tract and the major portion is excreted in the urine in the form of urea. Clinical and laboratory data indicate that the compound has a high therapeutic ratio, and to date adverse effects of importance have not been reported in situations where doses much higher than those recommended have been employed. Skin rashes have been seen but only in a very few of the patients receiving the drug.

Indications and Contraindications

Drugs possessing sedative and hypnotic properties are widely used and misused. The legitimate indications for these agents have been well defined (table 3). The more important known contraindications to their use are summarized in table 4. A certain amount of discretion should be employed in applying the information contained in table 4, since several of the contraindications are relative rather than absolute and experience with the newer drugs has not been sufficient to define their limits of usefulness.

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The Cardiac Glycosides in Medical Practice

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In 1785, William Withering, that astute English physician who introduced the use of digitalis into medicine, wrote, "It has power over the motion of the heart, to a degree yet unobserved by any other medicine, and that this power may be converted to salutary ends." Through a century and three-quarters of medical progress this statement has remained unchallenged. Modern studies on the metabolism of the heart at a cellular level have added support to the beneficial effect of the digitalis glycosides on the metabolism of the cells of the failing heart. They have reaffirmed our faith in the wisdom of therapy with the digitalis glycosides and opened new vistas for future investigations.

The purpose of this essay is to summarize our present knowledge concerning the action of the digitalis glycosides and to discuss the choice of the various glycosides in congestive heart-failure.

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Response of the Heart to Digitalis

The primary action of digitalis is on the heart. Its action on the myocardium may be conveniently divided into three components: (1) blocking of atrioventricular conduction, (2) increasing the contractility of the heart muscle, and (3) cardiac slowing, direct and through vagal stimulation. Digitalis was observed first to diminish atrioventricular node conduction by Mackenzie in 1911. With Cushny he showed that after digitalization the impulses from the fibrillating auricle no longer reached the ventricles. The drug produces, therefore, a partial atrioventricular block. Just how the glycosides act on the conduction is not known. Stroud and VanderVeer in 1937 expressed the view that the glycosides unite with cholesterol in the cardiac cells, forming cholesterides, and exert their action in this form. Sodium and potassium ion exchange in the myocardium effecting a more favorable potassium ion concentration has been suggested as the possible mechanism of action (Wood and Moe, 1942). More work is neces-

sary before an adequate explanation of this response will be forthcoming.

The glycosides of digitalis depress conduction in the heart. There is a lengthening of the refractory period in therapeutic doses. The diminished conductivity is most noticeable in the atrioventricular node.

The effect of digitalis on the refractory period of the different cardiac tissues is not uniform. Méndez and Méndez in 1953 studied the effect of digitalis glycosides differentially on auricular tissue, auriculoventricular propagation tissue, and ventricles in the heart of the dog. When the auricular tissue maintained its vagal innervation the glycosides decreased the refractory period of the auricles. The refractory period of auriculoventricular propagation increased progressively until the glycosides produced complete atrioventricular block. This is due to an action on the refractory period of the atrioventricular node. The refractory period of the ventricular muscle decreased under the influence of therapeutic levels of the glycosides. Toxic levels further decreased the refractory period until the ventricle was exposed to concentrations near those which initiate ventricular fibrillation.

It is likely that the glycosides affect the "margin of safety" of the atrioventricular conduction tissue. There is probably a diminution in the stimulus for propagation, i.e., the action potential. Further, the threshold to stimuli in the tissue ahead of the oncoming impulse may increase. Thus, impulses may die out in the atrioventricular conducting tissue and not reach the ventricles. In the toxic phase of atrioventricular block elicited by the glycosides, Méndez and Méndez suggested that the speed of conduction also diminishes markedly.

Digitalis increases the force of the systolic contraction in the dilated heart. The systolic shortening of the muscle fibers is greater and more prolonged. Hence the cardiac output is increased. Also, the ventricles fill more completely in diastole, increasing the force of ventricular systole by increasing the initial length of the muscle fibers.

In 1938 Cattell and Gold[1] answered the question of whether the increased contractility of the heart is produced directly or only indirectly through the action of digitalis on conduction and slowing. They used the papillary muscle of the right ventricle of the cat's heart. It was set up on an isometric lever and driven at a fixed rate. Its tension was measured photographically. When the papillary muscle began to fail, ouabain, a cardiotonic glycoside, was added to the bath in concentrations which are available in therapeutics; these were as small as 1 to 75 million. Under influence of the drug the tension rose and remained in that state for several hours. Gold and Cattell stated that "no other chemical material is known which produces such definite and sustained increase in the systolic force of the mammalian heart muscle." A typical effect is seen in figure 1. It is concluded, therefore, that digitalis does directly increase the force of contractility of the heart.

Krop in 1944 showed that epinephrine augments the systolic force of contraction of mammalian cardiac muscle. The xanthine bases such as theophylline are ineffective in this respect except in concentrations not attainable in therapeutics.

Wollenberger in 1947 demonstrated the specificity of the cardiotonic glycoside ouabain for cardiac tissue by manometric measure-

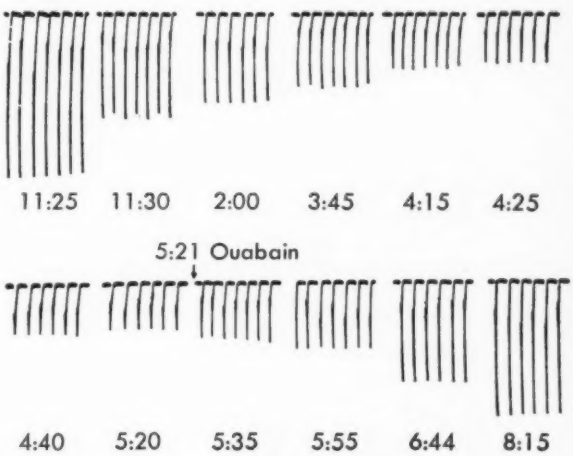

FIGURE 1. Effect of cardiotonic glycoside on the systolic force of mammalian heart muscle.

From CATTELL, McK. and GOLD, H.: Digitalis on cardiac muscle. J. Pharmacol. & Exper. Therap. 62:116, 1938.

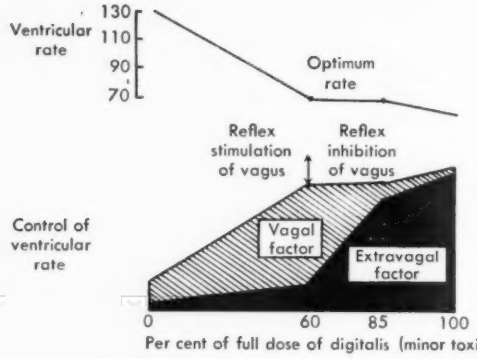

FIGURE 2. Schematic representation of the mechanism by which digitalis slows the ventricular rate in heart-failure with auricular fibrillation.

From GOLD, H. ET AL.: Physiological adaptations in cardiac slowing by digitalis and their bearing on problems of digitalization in patients with auricular fibrillation. J. Pharmacol. & Exper. Therap. 67:224, 1939.

ment of the oxygen uptake in tissue slices. He noted that ouabain in concentrations 2 to 3 times 10^{-7} molar increased the oxygen uptake of a guinea pig's heart muscle in the presence of glucose or lactate. The maximal increase was 50 per cent. At higher concentrations a depression of oxygen consumption followed the increase. Among the various other tissues studied, brain alone responded similarly; however, it was only 20 per cent as sensitive as cardiac muscle.

The third action of digitalis on the heart is the slowing of the cardiac rate. This action has as least two components, a direct effect on the heart muscle itself and a stimulation of the vagal center apparently mediated through the carotid sinus mechanism. In the same person with heart-failure the vagal and extravagal actions will depend on the dose of digitalis administered. Small doses produce cardiac slowing mainly by vagal action. This action of the drug is abolished by large doses of atropine. When the heart is digitalized and the optimal effect of the drug is produced, the extravagal slowing of the heart is as important a factor in the effect as the vagal action. The extravagal action is not abolished by atropine. Modell and associates in 1941 showed that in patients with heart-failure and auricular fibrillation under digitalis therapy, exercise would increase the pulse rate to 160 or 180 if the slowing was vagal only. If the slowing was extravagal also, exercise seldom would accelerate the pulse above 100. The observation bespeaks the increase of digitalis dosage in persons who have palpitation and dyspnea when active but are comfortable at rest.

The vagal and extravagal effects of digitalis in cardiac slowing are shown in figure 2.

Enzymatic Action of the Cardiac Glycosides

It has been stated previously that the cardiac glycosides increase the oxygen utilization of cardiac tissue. The action depends on the intactness of the muscle fibers, for it has been found that ouabain is 100 times more active on heart tissue slices than on tissue homogenates. Wollenberger[2] in 1951 demonstrated that the cytochrome system in cardiac tissue is not sensitive to ouabain. Other studies have shown that anaerobic glycolysis in cardiac tissue is not affected by the cardiac glycosides. The target enzyme system within the myocardium which appears to be involved in the activity of the cardiac glycosides is the adenosine triphosphate (ATP)-adenosine triphosphatase (ATPase) system. Wollenberger's[3] studies indicate that the cardiac glycosides facilitate the utilization of ATP by the contractile mechanism of the heart.

In cardiac deficiency states there appears to be a diminished supply of ATP available for the contractile mechanism. If this is due to diminished available energy for ATP synthesis, digitoxin, by increasing oxygen uptake of the tissue, will increase the available energy for this function. Studies by Read and Kelsey in 1957, using DIGOXIN®, suggest that this cardiac glycoside might enhance the contractile response of heart muscle at the expense of relaxation by activating the myokinase reaction (ADP-ATP). If the deficiency is due to accelerated breakdown of ATP owing to ATPase activity, digitoxin serves as an ATPase inactivator, thus sparing ATP (Proctor and associates, 1955).

Further, the cardiac slowing evoked by digitoxin is not dissimilar to that produced by acetylcholine, i.e., slowing of conduction

and atrioventricular node delay. Also, each agent releases intracellular potassium from the heart. The inhibition of cholinesterase extends the action of acetylcholine. Proctor and co-workers in 1955 demonstrated that digitoxin is capable of competing with cholinesterase and thus its effect on conduction in the heart may involve this component.

ATPase and cholinesterase are enzymes in which sulfhydryl groups appear to be critical. They are therefore sensitive to peroxides. The lactone group in digitoxin is capable of forming peroxides in the presence of molecular oxygen. Polarographic studies by Proctor and associates in 1955 showed that digitoxin can take up oxygen from solution and form a corresponding peroxide which is a more potent inhibitor of ATPase and cholinesterase. This hypothesis gained further evidence from the fact that cysteine reversed the inhibition of ATPase by digitoxin under aerobic conditions.

Another enzyme, ATP deaminase, which deaminates ATP, has been demonstrated in the rabbit's heart. This enzyme could affect the balance of ATP synthesis and breakdown in the heart. Proctor and associates showed that digitoxin inactivates ATP deaminase.

Thus the studies recorded have provided a tentative hypothesis for the action of the cardiac glycosides on an enzymic level, the principal postulates of which are as follows:

1. Increased oxygen utilization for greater energy expenditure and ATP synthesis.
2. Slowing of cardiac conduction through inhibition of cholinesterase.
3. Blocking rapid dissipation of ATP through ATPase inhibition.
4. Preservation of ATP balance by inhibition of ATP deaminase.

Effect of Digitalis on the Coronary Circulation

Until comparatively recently the action of digitalis on the coronary circulation was a polemic subject. Voegtlin and Macht in 1913 observed that digitalis caused constriction of the isolated coronary artery and suggested that it might therefore increase cardiac pain in patients subject to angiospastic disease. Fenn and Gilbert in 1932 observed an increase in cardiac pain when digitalis was administered to patients with angina pectoris.

Gold and associates in 1938 studied the problem critically and reached the opposite view. Their evidence appears crucial. They selected 120 patients who did not have congestive heart-failure but who experienced cardiac pain with physical effort. These persons were given therapeutic doses of digitalis and placebos alternately. In 15 per cent of the patients receiving digitalis, cardiac pain increased, and in 30 per cent a diminished incidence of cardiac pain was recorded. The results were strikingly similar when a placebo was given instead of digitalis. Gold concluded, "In view of the fact that the patients of this series were presumably unusually susceptible to cardiac ischemia, the results indicate further that digitalis even in large doses rarely, if ever, produces effective constriction of the coronary arteries in man."

The matter, therefore, appears to be settled for the present that digitalis does not produce a demonstrable effect on the coronary arteries in man *in situ*. Therefore the drug is available in heart-failure complicated with susceptibility to anginal pain.

Effect of Digitalis on the Vomiting Center

It is well established that in many persons digitalis produces nausea and vomiting. As this effect will attend the intravenous administration of digitoxin, it is not due entirely to gastrointestinal irritation. Gold and associates[4] in 1952 studied extensively the emetic action of digitalis in man. They observed that the gastrointestinal toxicity of the various cardiac glycosides exhibits a latent period of 10 hours in some cases. This has been one of the reasons for the assumption that the effect is central and not local. Administration of the glycosides intravenously or intramuscularly demonstrated that a more pronounced cardiac effect could be achieved with much less gastrointestinal distress. Gold has expressed the view that these findings do not justify the use of parenteral instead of oral digitalis glycosides. However, it is possible to achieve a more favorable cardiac response with less

emetic action in some cases by the parenteral use of the glycosides.

Digitalis stimulates the vagal center reflexly. The vomiting center lies adjacent to this brain center, and the action of digitalis stimulates it simultaneously. Hatcher and Weiss, in studies conducted in 1922 and 1927, found that direct application of the drug to the floor of the fourth ventricle did not elicit emesis. Dresbach and Waddell in 1939 showed that the emetic action persisted in the dog after vagotomy, stellate ganglionectomy, thoracic sympathectomy, and spinal cord section at the seventh cervical level. Thus all afferent fibers below the neck were blocked. This also seems to contradict the view expressed by Hanzlik and Wood in 1929; these workers suggested that the liver or some other abdominal viscus is the site of the emetic action.

Complete interpretation of the mechanism of action awaits further experimentation. The preponderance of evidence at present points to a direct stimulant effect of the drug on the vomiting center. The peripheral component of gastrointestinal toxicity undoubtedly contributes to the central effect.

Borison and Wang, in their comprehensive review of the physiology and pharmacology of vomiting, published in 1953, concluded that the digitalis glycosides evoke vomiting by acting at more than one receptor site. They stated the opinion that the central site of emetic action is the medullary chemoreceptor trigger zone, and, further, that the local irritating action on the gastrointestinal tract is probably insignificant under most circumstances.

Absorption and Excretion of Digitalis

Digitalis and its preparations are absorbed from the gastrointestinal tract. There is no convincing evidence that the alimentary juices affect the glycosides deleteriously. Absorption usually is complete in six to eight hours. Gold and his associates have shown that the principal glycoside of digitalis, digitoxin, is completely absorbed from the gastrointestinal tract. Destruction by the liver has also been excluded, since the oral and intravenous doses of the glycoside are nearly identical. Gitoxin and gitalin are less effectively absorbed.

The embryonic heart of the duck is extraordinarily sensitive to the cardiac glycosides. Friedman and co-workers used it in 1949 to study the excretion of digitoxin in man. Five persons were given 1.2 mg. of digitoxin. In the first 24 hours, 7 per cent was excreted in the urine. Somewhat less appeared in the urine on the second day, and still a smaller quantity was excreted the third day; 14 per cent of the glycoside administered was excreted during the first three days. Continuing their studies of the renal excretion of digitoxin, in 1952 Friedman and associates observed that patients with acute left ventricular failure excrete digitoxin as efficiently as do normal persons of the same age group. However, addition of right ventricular failure diminishes the renal excretion of digitoxin for a period of 24 hours. Cardiac patients who were compensated were found to excrete digitoxin at the same rate as normal persons, or about 30 to 40 per cent of the daily dose. When toxicity to digitoxin is manifested, more than twice as much digitoxin is excreted. Friedman and coworkers interpreted their findings as indicating that the probable maximal capacity of the body to degrade digitoxin is about 50 μg. per day.

Geiling and associates in 1953 studied the fate of C^{14}-labeled digitoxin in three patients with cardiac insufficiency. Their findings agree with those of Friedman and associates in the main, i.e., the kidney is the major route of digitoxin elimination. Marked excretion occurs during the first two days. Six to 10 per cent of the labeled drug was excreted as unchanged digitoxin, and the remainder as metabolic products of the glycoside. Of special interest is the persistence of small quantities of digitoxin in the urine as long as 40 days after the administration of one dose. It is again suggested that the cumulative effect is associated with its persistence in the body.

The fate of the digitalis glycosides in the body is not completely understood. The glycosides accumulate and then undergo a rather uniform rate of degradation for long periods. This has great clinical advantage. Once the heart is digitalized by repeated dosage, with cumulative effect, a so-called maintenance dose

may be given. For the average patient this is 100 to 200 mg. of the powdered leaf. This represents the amount destroyed and excreted daily. The degradation is believed to occur in the liver.

Toxic Manifestations of Digitalis

William Withering keenly observed the toxic manifestations of digitalis. There are numerous cases of digitalis poisoning owing to failure to recognize the danger signals. In most instances only doses that produce some minor toxic symptoms will achieve the full therapeutic effect of digitalis. The most frequent toxic symptoms are nausea and vomiting, and when they persist the dosage should be reduced.

Signs and symptoms of digitalis intoxication do not occur in regular sequence. Headache and nervous irritability may precede or accompany gastrointestinal distress. Greenish-yellow vision and flickering sensations are common. Visual symptoms are a frequent and almost always a faithful symptom of intoxication in a patient receiving digitalis. Abdominal pains, paresthesias, tingling of extremities, and facial neuralgia also have been noted.

Cardiac manifestations that may occur are extra ventricular systoles resulting from hyperirritability of the heart. These may pass into ventricular fibrillation and lead to death. Intravenous use of the pure glycosides must be enjoined with great caution owing to the incidence of toxic manifestations.

Berger in 1952 observed a case of thrombopenic purpura following digitoxin therapy. Other drugs such as mercurial diuretics did not elicit the blood dyscrasia. This is a rare case but is considered important in view of the seriousness of the toxic manifestation.

Choice of a Digitalis Preparation

In choosing a satisfactory digitalis preparation there are three important considerations: (1) the latent period before action, (2) the rate of dissipation, and (3) the rate and completeness of absorption. For routine use the official digitoxin appears to be the drug of choice (figure 3). The dose for complete digitalization is about 1.25 mg. Absorption is complete orally, and its standardization has been effectively accomplished. Complete effect is achieved in between 6 and 10 hours. For an acutely decompensated patient this latent period is lengthy and a single intravenous injection of 0.5 mg. of ouabain (strophanthin) is indicated. The effect appears within 10 to 30 minutes, and more of the drug may be given, 0.1 mg. at half-hour intervals, up to a total of 1 mg. The period of dissipation for ouabain is short; that for digitoxin is long. Ouabain is not available for oral use.

The advantage of a short period of dissipation is obvious if toxic manifestations occur, as the rapid degradation and excretion of the drug may soon terminate the toxic effects. With digitoxin they may persist for long periods due to the drug's prolonged period of action before dissipation. This, of course, is an advantage in the routine use of the drug for maintenance therapy. The effect of a single dose of digitoxin may last 8 to 12 days.

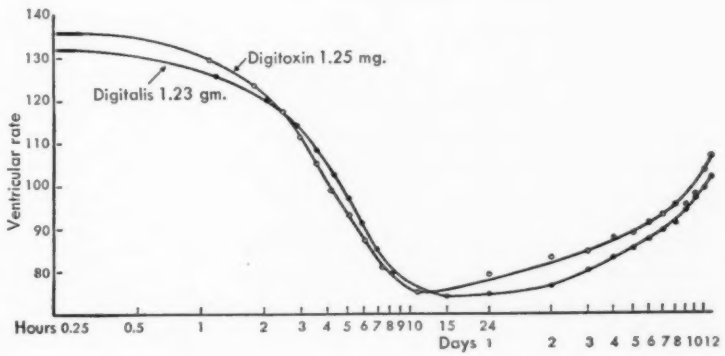

FIGURE 3. Comparison of oral digitoxin and digitalis in nine patients with heart-failure and auricular fibrillation. The drug was given in one dose. Time is charted in hours after the dose. Note the similarity in speed of absorption and duration of action of digitalis and digitoxin.

From GOLD, H.: Pharmacologic basis of cardiac therapy. J.A.M.A. 132:547, 1946.

TABLE 1

APPROXIMATE DOSES OF VARIOUS CARDIOACTIVE PREPARATIONS FOR ORAL AND INTRAVENOUS USE*

PREPARATION	INITIAL DIGITALIZATION				DAILY MAINTENANCE	
	Oral		*Intravenous*		*Oral*	
	Average	Range	Average	Range	Average	Range
Digitalis	1.2 gm.	1-2 gm.			0.15 gm.	0.05-0.30 gm.
Digitoxin	1.2 mg.	1-2 mg.	1.2 mg.	1-2 mg.	0.15 mg.	0.05-0.30 mg.
Acetyl digitoxin	2.0 mg.	1.5-2.5 mg.	1.5 mg.	1.3-2.0 mg.	0.3 mg.	0.1-0.6 mg.
Gitalin (amorphous)	5.0 mg.	4-8 mg.			0.5 mg.	0.25-1.0 mg.
Digoxin	3.0 mg.	1-4 mg.	1.0 mg.	0.8-1.6 mg.	0.5-0.75 mg.	0.25-1.0 mg.
Lanatoside C	6.0 mg.	5-10 mg.	1.6 mg.	1.2-1.6 mg.	1.0 mg.	0.5-2.0 mg.
Ouabain			0.8 mg.	0.5-1.0 mg.		
Acetyl strophanthidin			0.6 mg.†	?		

*Adapted from *Circulation*, August 1955, p. 297.

†Maximal dose for a single injection, to be diluted and administered in not less than five minutes. Average total dose for full digitalization is approximately 1.2 mg.

Digoxin obtained from *Digitalis lanata* is rapidly active and has a short dissipation period. It is absorbed by the oral route but not completely. It has been claimed that medication with Digoxin affords greater freedom from toxic manifestations than does medication with digitoxin. It is doubtful if this claim can be substantiated in the general run of cardiac patients. Work by Batterman and DeGraff in 1947 indicates that digitoxin stands at no disadvantage compared with Digoxin. The average digitalizing dose of Digoxin is from 1 to 2 mg., and the maintenance dose is 0.75 mg.

Amorphous gitalin is gaining prominence as a cardiac glycoside. Like Digoxin, it has a short period of dissipation. Batterman, DeGraff and Rose[5] found that gitalin exhibited a margin of safety greater than digitalis leaf, digitoxin or Digoxin. Absorption was dependable in their series of patients. On the average, for therapeutic effect, 100 mg. of digitalis leaf was equivalent to 0.46 mg. of gitalin. On the other hand, for toxic manifestations, 100 mg. of digitalis was equivalent to 0.65 mg. of gitalin. Gruhzit and Farah observed that gitalin did not exhibit a greater margin of safety (between the therapeutic and toxic doses) than did the other cardiac glycosides. Their studies were conducted on the failing heart of the dog in heart-lung preparations. Table 1 gives approximate doses of cardiac glycosides for oral and parenteral therapy.

Summary

The glycosides of digitalis remain the drugs of choice in treatment of congestive heart-failure at present. Their isolation and purification have rendered therapy less difficult and more effective. Our present knowledge of their mechanism of action at an enzyme level has borne testimony to the soundness of their use in the treatment of congestive heart-failure.

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Cholinergic and Anticholinergic Drugs

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Cholinergic† Drugs

DRUGS which simulate the pharmacologic action of acetylcholine are designated as parasympathomimetic or cholinergic. They fall into three groups according to their mechanism of action: (1) the choline esters, (2) the cholinesterase inhibitors, and (3) the naturally occurring alkaloids.

Choline esters—The choline esters are chemically similar to acetylcholine and exhibit comparable effects on secretory gland cells and smooth muscle. The only clinically important members of this group are URECHOLINE® and MECHOLYL®. Ordinarily these drugs are effective only by the parenteral route, although Urecholine occasionally may be effective orally. They should *never* be administered intravenously.

Urecholine is useful in circumstances in which stimulation of peristalsis is desired—e.g., adynamic ileus, urinary retention and gastric atony—provided mechanical obstructions are ruled out.

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†The word "cholinergic," meaning "affected by choline," designates nerve endings which release acetylcholine to accomplish their neuroeffector transmission; thus it is incorrect to apply the term to drugs. However, it is so used here in deference to established practice, especially since there is no good generic term in general use to designate drugs mimicking the action of acetylcholine.

Mecholyl is used occasionally in treatment of unresponsive supraventricular tachycardia, but considerable caution must be exercised since it produces strong vagal stimulation to the heart. The primary use of this drug, however, is to distinguish cardiospasm (achalasia) from other causes of esophageal obstruction. In the presence of cardiospasm a subcutaneous injection of 5 to 10 mg. of Mecholyl is followed by a subjective sensation of substernal pressure and objective roentgenographic or kymographic evidence of a mass contraction of the esophagus.

Cholinesterase inhibitors—Such drugs as physostigmine, neostigmine (PROSTIGMIN®) and di-isopropyl fluorophosphate (DFP) interfere with the enzyme systems responsible for the inactivation of acetylcholine. They are therefore parasympathomimetic by potentiation of acetylcholine. By virtue of this action, neostigmine (Prostigmin) is the primary agent in treatment of myasthenia gravis. Its use in this disorder is based on an increase in acetylcholine at the motor end-plate of striated muscle and consequent increase in neuromuscular transmission. It is also used, as is Urecholine, in treatment of hypoperistaltic states such as adynamic ileus. As a diagnostic agent, Prostigmin has been used to distinguish functional amenorrhea from pregnancy; administration of the drug for a period of three days is followed by menstrual flow if the patient is not pregnant.

Di-isopropyl fluorophosphate (DFP) is a very potent inhibitor of cholinesterase and is used as a miotic agent in treatment of increased intraocular tension, as in glaucoma.

Naturally occurring alkaloids—Pilocarpine, the only important drug in this group, evokes parasympathomimetic action although it is neither a choline ester nor an inhibitor of cholinesterase. Its primary use is as a miotic agent in treatment of increased intraocular tension. It has also been recommended, along with Urecholine and neostigmine, as an adjunct to the ganglionic blocking agents used in treating hypertension, in order to overcome undesirable bladder and bowel impairment.

Cholinergic drugs are contraindicated in conditions in which parasympathetic activity would be undesirable, e.g., in asthma, hyperthyroidism and certain types of heart disease.

Anticholinergic Drugs

An anticholinergic drug is one which opposes the actions of nerves whose effects are transmitted by the release of acetylcholine. These drugs may be naturally occurring (alkaloids of belladonna) or synthetic (ANTRENYL®, BANTHĪNE®, CANTIL®, CENTRINE®, DACTIL®, DARBID®, DARSTINE®, DIBULINE®, ELORINE®, MONODRAL®, PATHILON®, PAMINE®, PIPTAL®, PRANTAL®, PRO-BANTHĪNE® and TRAL®).

Clinical pharmacology—Gastrointestinal motility—All anticholinergic drugs inhibit gastrointestinal propulsive motility when given in adequate dosage; the effective oral dose is accompanied by some side effect, usually xerostomia. The motor-inhibitory effect is primarily on the small intestine. Although the clinical use of anticholinergics as antispasmodics is based on the antimotility effect as demonstrated by radiographic or kymographic methods, there is no physiologic or clinical evidence that these drugs can correct disordered motility or counteract spontaneous "spasms" of the intestine.

Gastric secretion—Anticholinergic drugs in adequate dosage diminish the basal secretion of acid as well as that stimulated by histamine and by cholinergic drugs, but they have little effect on the acid secreted in response to food or to insulin hypoglycemia. Hence the most rational application of the antisecretory properties of anticholinergics is to abet the action of antacids in dealing with the night secretion in patients who have duodenal ulcer. The fact that anticholinergics do not prevent the gastric secretory response mediated by the vagi during hypoglycemia makes it illogical to speak of these drugs as "performing a medical vagotomy."

Pancreatic secretion—Large doses of anticholinergics administered parenterally may reduce external pancreatic secretion. It is not known whether the inhibitory effect, when it occurs, is directly on the pancreas by parasympathetic block or indirectly by reduction of acid gastric content entering the duodenum to initiate the secretin mechanism.

Management of gastrointestinal disease—Esophagitis—This condition is generally a result of reflux of gastric contents into the esophagus and frequently is associated with hiatus hernia. The use of anticholinergics in any physiologically effective dosage probably is contraindicated for at least three reasons: (1) Disintegration of the tablet in the distal esophagus may cause local irritation to the already inflamed mucosa; (2) inhibition of esophageal motility and reduced intra-esophageal pressure may abet the reflux tendency; (3) inhibition of gastric emptying may prolong the period of reflux.

Cardiospasm—This condition is currently regarded as a result of loss of parasympathetic transmission to the esophageal musculature, and anticholinergics would theoretically be contraindicated. In practice it has been found that they are of no benefit.

Peptic ulcer—In esophageal ulcer the same principles apply as in esophagitis. Gastric ulcers in the body of the stomach generally occur in older persons in whom the level of acidity is low, and anticholinergics are undesirable for this group. Ulcers in the antrum resemble duodenal ulcers in their pathologic physiology and their response to an ulcer regimen, and are treated accordingly. In symptomatic management of duodenal ulcer, controlled studies have failed to demonstrate any superiority of the synthetic anticholinergics over the naturally occurring forms, and some observers report equally good results without an anticholinergic. Rapid relief of pain has been claimed for almost every one of the synthetic anticholinergics, but there is no evidence that the belladonna alkaloids are less effective in this regard. Substituting the synthetic for the naturally occurring anticholinergics in the standard regimen does not accelerate the rate of healing of duodenal ulcers significantly. Prolonged administration of anticholinergics does not favorably alter the ultimate course of duodenal ulcer; on the contrary, dependence on these drugs alone may engender complications.

Pancreatitis—Anticholinergic drugs in large parenteral doses may be used in an attempt to relieve pain in acute and chronic pancreatitis, but they do not alter the course of the disease.

Functional gastrointestinal disturbances—The only entity in this category which has been the subject of controlled investigation is the irritable colon syndrome; anticholinergic medication did not give better results than did placebos.

Dosage—The physiologic dose of any anticholinergic is that which produces a sensation of dryness in the buccal or pharyngeal mucous membranes. Occasionally one of the other side effects such as dysuria or blurring of vision may occur before xerostomia. The dose required to produce side effects varies and is often some multiple of the unit dose (amount per tablet or capsule) and of the dose recommended in the promotional literature. The interval between doses is an individual matter; generally the effects are more dependable if the drug is administered sufficiently in advance of meals to permit the material to traverse the upper intestine before ingested food can mix with it; this may vary from 20 minutes to an hour. It is probably this delaying action of food on the absorption of anticholinergics that defeats the purpose of the so-called long-acting or slow-release forms, because the drug apparently does not get into the blood in sufficient concentration to exert useful pharmacologic action.

Side effects—The symptoms that are designated as side effects of anticholinergic drugs are usually physiologic effects indicative of interference with cholinergic functions other than those at which the therapeutic effort is aimed. The most common ones are xerostomia, disturbances of accommodation, dysuria and constipation. One can usually control them by adjusting the dose or by other appropriate measures. In approximately 10 per cent of cases in which these drugs are administered, they must be discontinued because the undesirable manifestations take the form of an intolerance or even a toxicity; examples of such effect are nervousness, insomnia, nausea and dermatitis.

Specificity—In a given patient, anticholinergic drugs may affect one of the cholinergic functions more readily and more prominently than another, but the assertion that certain of

these drugs are consistently selective for a particular gastrointestinal function or a limited portion of the alimentary tract has not been substantiated. Thus there is no "anticholinergic of choice" for any specific gastrointestinal disturbance.

Comment—The proved accomplishments of anticholinergic drugs are far less impressive than those claimed. If anticholinergic action were as beneficial in various digestive disturbances as the promotional literature would have us believe, the naturally occurring anticholinergics would suffice because none of the synthetic preparations are superior to them. Further, it would not be necessary to combine these drugs with sedatives, as is done almost routinely.

The principal indication for anticholinergics is their use in conjunction with antacids to reduce the night secretion in duodenal ulcer. Anticholinergics as the sole treatment of peptic ulcer are not only ineffective but they may also be dangerous. For the most intense and prolonged action, these drugs should be administered to the patient 20 minutes to an hour before meals.

Cleveland Assembly Motion-picture Schedule

Monday, November 10

2:00 to 5:00 P.M.: Selected movies.

Tuesday, November 11

9:00 to 10:00 A.M.: Selected movies.

10:00 A.M.: Surgical Treatment of Prolapse of the Rectum—William A. Altemeier, M.D., University of Cincinnati College of Medicine, Cincinnati

10:32 A.M.: The Repair of Esophageal Hiatal Hernia Using the Abdominal Approach—James H. Growdon, M.D., University of Arkansas School of Medicine, Little Rock

11:01 A.M.: Indications and Technic of Right Hepatectomy—John R. Reynolds, M.D., University of Illinois College of Medicine, Chicago

11:36 A.M.: Transabdominal Adrenalectomy for Endocrine Disease—Edward H. Ellison, M.D., Ohio State University College of Medicine, Columbus

2:00 P.M.: Choledochojejunostomy for Restoration of Biliary Drainage—Charles G. Child, III, M.D., Tufts University School of Medicine, Boston

2:31 P.M.: Common Duct Stones—Robert M. Moore, M.D., University of Texas School of Medicine, Galveston

3:00 P.M.: The Surgical Treatment of Pancreatic Pseudocysts—David M. Hume, M.D., Medical College of Virginia, Richmond

3:38 P.M.: Exploration of Pancreas for Islet Cell Tumor—Professor Ian Aird, M.D., Ch.M., M.B., Ch.B., University of London Faculty of Medicine, London

4:07 P.M.: Arteriovenous Fistulas of the Femoral and Innominate Vessels—John M. Howard, M.D., Atlanta

4:32 P.M.: Surgical Treatment of Bronchogenic Carcinoma—George V. Brindley, Jr., M.D., University of Texas Post-Graduate School of Medicine, Temple

Wednesday, November 12

9:00 A.M.: Vaginal Hysterectomy—Mr. W. Hawksworth, O.B.E., F.R.C.S., F.R.C.O.G., United Oxford Hospitals, Oxford, England

9:37 A.M.: Lesions of the Fallopian Tube—Newell W. Philpott, M.D., McGill University Faculty of Medicine, Montreal

10:09 A.M.: Emergency Surgery of the Acutely Injured—James D. Hardy, M.D., University of Mississippi School of Medicine, Jackson

10:42 A.M.: Caudal Pancreaticojejunostomy for Chronic (Relapsing) Pancreatitis—John A. Schilling, M.D., University of Oklahoma School of Medicine, Oklahoma City

11:07 A.M.: Cardiac Arrest—Henry Swan, M.D., University of Colorado School of Medicine, Denver

11:35 A.M.: Aneurysms of Abdominal Aorta. Surgical Considerations Based on Analysis of 350 Resected Cases—Michael E. DeBakey, M.D., Baylor University College of Medicine, Houston

2:00 to 5:00 P.M.: Repeat of films shown Tuesday morning

Thursday, November 13

9:00 A.M.: Coarctation of the Aorta—Earle B. Mahoney, M.D., University of Rochester School of Medicine, Rochester, New York

9:30 A.M.: The Story of Renal Calculi—Charles C. Higgins, M.D., Cleveland Clinic and Cleveland Clinic Hospital, Cleveland

10:03 A.M.: Safe and Conservative Treatment of Lesions of the Female Breast—W. Emory Burnett, M.D., Temple University School of Medicine, Philadelphia

10:36 A.M.: Cholecystectomy and Operative Cholangiography—Joel W. Baker, M.D., University of Washington School of Medicine, Seattle

11:08 A.M.: Hernias in Infants and Children—Colin C. Ferguson, M.D., University of Manitoba, Winnipeg

11:40 A.M.: Transportation of the Injured—George J. Curry, M.D., Hurley Hospital, Flint, Michigan

Analgesic Agents and the Control of Pain

E. G. GROSS AND H. H. KEASLING*

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THE title of this article implies that analgesic agents are but one method to be utilized in the control of pain. We agree with this thesis completely.

We will use the term "analgesic" to denote any chemical for the relief of pain which produces its effect by means other than reduction or removal of the causative factor or factors and without producing unconsciousness. Examples are salicylates,† "coal tar analgesics," opiates, and synthetic drugs similar pharmacologically to opiates. This definition of an analgesic is not without objection but it is sufficiently clear for the present purpose. Certainly it is less polemic than any definition of pain that can be devised. Pain has been variously characterized as peripheral nerve impulses, other levels of nervous activity up to conscious sensation, reaction to the sensation, and even as a quality, like goodness or justice; any attempt on our part to endorse a given hypothesis cannot serve the purpose of this discussion. The "hurt" that the patient describes, whatever its neurophysiologic basis, is the concern of the physician, and it is clearly his duty to do all in his power to relieve the complaint "I hurt."

E. G. GROSS

H. H. KEASLING

The best way to provide relief is by correction of the underlying pathologic process. The nitrites, for example, ordinarily represent the best relief for the pain of angina pectoris; such examples are legion. Analgesics should be utilized only when pain is not controllable by other means. We do not mean to imply that one should withhold analgesic medication from a patient in pain. Indeed, inadequate analgesic medication may increase the difficulty by destroying the patient's confidence in the physi-

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†We have classed the salicylates as analgesics even though there is evidence suggesting that their action in relieving the pain of neuralgia, myalgia and similar conditions may be due in part to reduction of edema, i.e., due to removal or correction of the causative factor.

cian. One must, however, as with any therapeutic agent, balance the expected benefits of therapy against the potential disadvantages and dangers. The discussion which follows is based on the assumption that other methods of pain relief have been considered and have either proved ineffective or been discarded on other grounds, and that the decision to use an analgesic agent has been made.

After deciding to utilize an analgesic agent, the physician next must choose the agent and mode of therapy. Perhaps the most important factor influencing his choice of analgesic is its ability to accomplish the desired degree of relief of pain. One must of necessity balance the potency of the agent against the liabilities of its use; these liabilities will be considered later. The "potency" of the agent, as here used, is independent of the amount (milligrams) of the agent used as the dose; instead it is a function of the intrinsic ability of the agent to relieve pain. General anesthetics, for example, can relieve any pain regardless of its intensity, and in this sense a general anesthetic (e.g., ether) is very potent.

We may group the common analgesics in three categories on the basis of potency: mild, intermediate and potent. Each class of agent has a ceiling of effectiveness; once this ceiling is reached, further increases in the size of the dose may alter the duration of effect but will not alter its intensity. An analgesic agent with a significantly higher ceiling of effectiveness would be a most desirable addition to the physician's armamentarium. In view of this ceiling of effectiveness it is essential that the physician judge the intensity of pain. He should consider the patient's complaint as well as the degree of trauma in forming this judgment and also should estimate the "suitability" of the patient's reaction to the pain.

These various factors influencing the use of analgesics emphasize that the pharmacologic properties of these agents are not of themselves sufficient to confer control of pain, in most situations. While it seems clear that morphine raises the pain threshold, this is only part of its action in the control of pain; the alteration in the patient's reaction to his pain may be as important or even more important. Regardless of the mechanism of morphine analgesia, the physician's concern is relief of pain in the individual patient. It is all too easy to regard the administration of a drug as sufficient relief of pain. Unfortunately the control of pain is rarely so easy. The physician must, in addition, evaluate the patient's psychologic status and treat these disorders simultaneously, because they are part and parcel of the syndrome "I hurt."

While lesser degrees of relief than the ceiling of effectiveness may be obtained by decreasing the dose of even the most potent agent, it is ordinarily preferable to use the least potent agent that will accomplish the desired effect. Tolerance appears to be diminished by use of the relatively less potent agents and, furthermore, addiction liability increases in general with increasing potency.

Once a given class of agent with regard to potency has been selected (mild, intermediate, potent), it is necessary to balance the other effects of the agents in that general class against the condition of the patient. Evaluation of these side effects of the analgesics requires a knowledge of the pharmacologic properties of the individual agents. Intensity of the side effects as well as effectiveness of analgesia are functions not only of the intensity of pain but also of the dose of analgesic. The optimal dose varies from situation to situation, but it is best to consider this complex problem in the light of the old maxim that one should always use the minimal effective dose; this principle is all too commonly ignored.

It is impossible to state *the dose* of an analgesic drug. It would seem far more desirable to utilize a small dose and repeat it if necessary after sufficient time has elapsed for maximal effect to develop. This method of therapy may frequently prove inconvenient for the physician, but the frequency with which such small doses provide adequate relief of pain with fewer side effects strongly recommends it. While, in general, one must increase the dose of an analgesic in proportion to the intensity of the pain, numerous factors may alter this simple relationship. An important one is the rapport between physician and patient. If the patient is convinced of the physician's

competence and sincere desire to relieve his pain, this may well reduce the amount of analgesic needed. The striking effectiveness of placebo medication has been demonstrated on numerous occasions. It is important that the physician recognize and utilize this therapy. In a study of the effectiveness of placebos, Batterman reported that 86 per cent of patients got occasional relief from placebos. Further, the 14 per cent who did not respond to placebos did not get relief from presumably effective analgesic medication. Perhaps this represents striking evidence of the relative importance of the physician and the patient's psychologic make-up in contrast to the pharmacologic properties present in the analgesic medication.

The mild analgesics, including salicylates, acetophenetidin and acetanilid, are administered only by the oral route. Their analgesic effects appear 15 to 30 minutes after administration and last three to four hours. They probably are the agents of choice in neuralgia, myalgia, headache and arthritic-type pains. Even though the degree of analgesia is mild, they offer the distinct advantage of lack of tolerance, and on this basis one should perhaps give them a trial in cases of chronic pain. If salicylates provide adequate analgesia they should be utilized as long as possible. Although it is often stated that these agents are ineffective in visceral-type pain, Houde and co-workers have shown significant analgesia with the salicylates in studies of the pain of cancer.

Indications for use of the paraminophenols (acetanilid and acetophenetidin) are similar to those of the salicylates except they should not be used for chronic administration because they may produce chronic poisoning by their tendency to form methemoglobin and sulfhemoglobin.

The intermediate and potent analgesics all resemble morphine to a greater or lesser degree, and it is convenient to discuss the properties of morphine and then contrast the other agents with it.

The primary therapeutic property of morphine is its ability to induce analgesia. Simultaneously, however, it produces a number of other effects commonly classified in therapeutics as side effects. The fact that all known potent and intermediate analgesics possess many of these properties, however, indicates that these effects are normal concomitants of analgesic agents and must represent fundamental drug actions. The variabilities to be noted later suggest that in the future one may hope for compounds lacking these effects.

In addition to analgesia, morphine produces sedation and a sense of well-being. These effects are ordinarily more pronounced in the patient who receives pain relief. Occasionally it may produce dysphoria, hypnosis or even coma. Nausea, emesis and vertigo are also common. Morphine affects smooth muscle throughout the body; in the gastrointestinal tract this is evidenced by relaxation of the stomach and spasm of the small and large intestines. These effects markedly diminish the practicability of oral administration of morphine, as the first increments of the dose absorbed produce the aforementioned gastrointestinal effects and, in addition, spasm of the pyloric sphincter. Thus the onset of effect in turn delays absorption of the remainder of the dose, diminishing the peak of effectiveness of a given dose and prolonging the duration of effect of orally administered morphine. The ureter, vesical sphincter and detrusor muscle are brought into spasm by morphine, leading to urinary urgency with simultaneous difficulty of micturition. Atropine counteracts these effects. The biliary duct also is brought into spasm, which is resistant to the action of atropine and necessitates the administration of nitrites, papaverine or theophylline ethylenediamine (aminophylline).

All of the analgesic agents in the intermediate and potent classes are contraindicated in the presence of increased intracranial pressure unless the patient's ventilation is carefully supervised. The induced respiratory depression leads to accumulation of carbon dioxide which in turn leads to dilatation of cerebral vessels and a further increase in intracranial pressure. One must exercise caution in administering these agents to patients having liver disease or acute renal damage, as these organs are important in the detoxication and excretion of the drugs. Morphine, because it

causes itching, should not be given to patients with pruritus.

One further disturbing "side effect" is respiratory depression. Animal experiments indicate that for a given degree of "analgesia" a fixed amount of respiratory depression is produced, regardless of the agent. Clinical experiments, while less exact, indicate a similar situation in man. Ordinarily, textbook statements about the variations in respiratory depression produced by the various agents are based on effects in patients having different intensities of pain; thus variable effects are obtained. Most anesthetists, however, note respiratory depression following the administration of any analgesic as preanesthetic medication. In ordinary use the degree of depression that *moderate* doses of these agents produce may not be of particular concern to the physician, but it is important in patients whose respiration is embarrassed because of a pathologic process or who suffer other insult to the respiratory mechanism. In these latter situations the additional depression the analgesic produces may be quite dangerous.

When dangerous respiratory depression follows the administration of intermediate or potent analgesics, ordinarily one can counteract it by administering one of the opiate antagonists, N-allylnormorphine (nalorphine, NALLINE®) or N-allylnorlevorphan (levallorphan, LORFAN®). These antagonists are specific for any analgesic of the intermediate or potent class, and they antagonize not only the respiratory depression but also the analgesia. Further, studies in both man and animals have demonstrated that the antagonists given in large doses are capable of inducing analgesia and respiratory depression in their own right. Therefore, one must give them with care in the treatment of analgesic-induced depression; overdosage of an antagonist may yield respiratory depression.

The effects of the opiate antagonists administered intravenously in treatment of analgesic-induced depression appear in about two minutes. It is best to give the antagonist by the intravenous route in small doses repeated at intervals as required to maintain satisfactory ventilation. Failure of improvement to occur in 5 to 10 minutes suggests the presence of depression induced by agents other than analgesics, in view of the specificity of these antagonists for analgesics. They are of no value in other types of depression. One must give them cautiously to suspected addicts, because in these patients the antagonists precipitate the withdrawal syndrome with great intensity.

The onset of morphine action varies with the route of administration, but even intravenously it may require as long as 20 minutes; peak effects ordinarily occur in 30 to 60 minutes. When morphine is given by other routes the effects are correspondingly slower to appear. They persist for three to four hours.

In excruciating pain such as experienced in myocardial infarction, one should give morphine intravenously. The physician must be sure to give a dilute solution slowly, since rapid injection of a concentrated solution may be quite depressant to the heart. Doses of 5 to 10 mg., repeated in 20 to 30 minutes if additional analgesia is required, are recommended. In situations of severe pain the delay in onset which follows the administration of morphine by other routes often leads to the administration of second and third doses before the peak of effect of the first dose is reached; with the relief of pain, the antagonistic action of pain on the effects of morphine is lost and the patient may evidence acute overdosage of morphine.

It would appear that in most situations a dose of from 6 to 10 mg. of morphine will give excellent results. Extensive clinical experiments have indicated that doses exceeding this level increase analgesia only slightly but increase the liability of side effects greatly. In special situations requiring larger doses, it would appear that doses in excess of 30 mg. per 70 kg. give no additional analgesia.

Morphine and all other potent and intermediate analgesics induce tolerance, and, further, show cross tolerance with each other.

The intermediate group of analgesics includes codeine and meperidine. Newer agents purportedly belonging in this class have not been evaluated sufficiently to assure their eventual status, although they show great promise at present. The most important difference be-

tween these compounds and morphine is in regard to the ceiling of effectiveness of analgesia. It appears that doses of codeine in excess of 65 mg. (1 gr.) do not produce an increase in analgesia and that at this level the effectiveness of codeine is no more than 50 per cent of that obtained with ordinary doses of morphine. The gastrointestinal effects which follow the administration of morphine occur much less frequently with codeine, but when they do occur they are qualitatively similar to those of morphine. The other side effects of morphine also are less common with codeine, except those referable to depression of the central nervous system. Respiratory depression, for example, appears to be a negligible factor in codeine therapy. The lack of sedation following administration of codeine indicates its undesirability in excitatory states. Addiction to codeine has been reported, but some conflict exists in the literature in this regard, particularly with ordinary medical use. Studies at the United States Public Health Service Hospital in Lexington, Kentucky, have shown that addiction to codeine is possible and that the drug will partially prevent the symptoms of morphine withdrawal in addicts.

Codeine is effective by all routes of administration, but the oral route usually is preferred. Combinations of codeine with mild analgesic agents are commonly used to relieve pain refractory to the mild analgesic agent alone. Such combinations offer the advantage that pain relief may be afforded by doses of codeine that are ineffective when given alone. We do not know of any controlled clinical experiments supporting this thesis, but there is abundant clinical impression in this regard.

Meperidine (DEMEROL®), while not a phenanthrene derivative, is nevertheless similar in pharmacologic properties to morphine. Again, there are several clinically important differences between it and morphine. We have classed meperidine as an intermediate agent in potency, although it may in fact lie between codeine and morphine with respect to ceiling of effectiveness. The amount of sedation seen in ordinary use of the drug further reflects this intermediate activity. As with codeine, assessment of its analgesic effects in animals is limited by convulsions. This same activity is perhaps reflected in the statement that meperidine addiction in man is characterized by the limitation of daily dose imposed by the appearance of convulsions. One may, however, utilize this decreased sedative effect of meperidine to advantage in many clinical situations. We wish to emphasize that meperidine induces respiratory depression, because of the common misconception to the contrary.

Meperidine differs from morphine with respect to actions in the gastrointestinal system. While spasm in both small and large intestines is the rule following administration of morphine, meperidine produces spasm in only the jejunum and duodenum. Both drugs reportedly cause a rise in intrabiliary pressure. Meperidine may be given by all routes of administration, although induration often follows subcutaneous injection.

The pharmacology of dihydromorphinone (DILAUDID®) is essentially that of morphine, except that it is 5 to 10 times as active as morphine on a milligram basis. The ceiling of effectiveness is, however, no greater than that of morphine. Duration of action is somewhat shorter than that of morphine, and spasmogenic effects are quantitatively less, so that when relief of shorter duration is required it may offer some advantage.

Methadone (ADANON®, DOLOPHINE®), while similar to morphine, reportedly is less sedative and less constipating and produces less nausea. Its oral effectiveness reflects the diminished gastrointestinal action. The relative lack of sedative action may make its use desirable in certain patients.

Levorphanol (levorphan, LEVO-DROMORAN®) is more potent than morphine on a weight basis but it has a similar ceiling of effect. Like methadone, it is less stimulant to the gastrointestinal tract and has the advantage of oral effectiveness. It produces sedation like that of morphine.

Alphaprodine (NISENTIL®) is a potent analgesic similar in action to morphine but it has a short duration of action. Onset and decline of its effects are rapid, making it particularly suited for relief of short duration.

We have oriented the preceding discussion

toward the use of analgesics in acutely painful situations. The phenomenon of tolerance plays a large role in their use when relief must be accomplished over a period of weeks or months. The possibility of "medical addiction" also must be considered in chronic situations in which it is expected that the agents will be withdrawn after extended administration. Although it would seem that "medical addiction" occurs only infrequently, on the basis of available reports of the United States Public Health Service Hospital, this may reflect the care that physicians ordinarily exercise in the prolonged use of these agents rather than an inherent lack of danger in the medical situation. In any event, if the illness is terminal the problem of addiction is of minor importance to the patient compared with the development of tolerance and the inability to obtain relief of pain from analgesics.

It would appear that tolerance is certain to develop in chronic situations. Therefore, the physician must consider carefully the means by which he may slow its rate of development and thereby delay the day when analgesic medication no longer is effective. The principal means to accomplish this seems to be the administration of mixtures of narcotics and antagonists on the one hand and the development of tolerance to pain on the other. Adaptation on the part of the patient appears the more successful method, since it allows less frequent administration of smaller doses of analgesics. The sympathetic physician can do much to foster a stoic attitude in his patient if he will spend the time required. He must convince the patient that he accepts the patient's report as the final authority on the pain and that he is sincerely concerned with doing his utmost to comfort the patient.

One method of analgesic medication employs the "narcotic wheel" of Dr. F. A. D. Alexander. The patient is informed that for each person a particular drug may be more satisfactory than any other drug, and in order to determine which is the most effective for him he will be given various drugs on successive days; he can then choose the one best suited to his needs. The various analgesics are administered for a day at a time, and at the conclusion of the rotation the patient is questioned as to his preferences. The reality of the differences noted by the patient may be questioned, but the attempt itself appears to be of great benefit.

In selected patients, demand dosage of analgesic medication may lead to reduction in daily narcotic dosage and thereby delay the development of tolerance. Dr. Alexander has stated that many patients who formerly took medication every four hours reduced their daily intake by as much as one-half when assured that a narcotic could be obtained whenever they desired. It appeared that when medication was given every four hours the patient accepted each dose available in order to prevent pain between doses, since nursing routine would not allow administration of the dose later if it was not accepted at the scheduled time. Further, if the patient was convinced that analgesic medication was always available, he tried to endure the pain a little longer, thus reducing the total narcotic intake further.

Dr. L. J. DeBacker has utilized a similar technic by offering weak and potent medication simultaneously to nonhospitalized patients. The patient is given tablets of APC® or APC with codeine, and also tablets of levorphanol, and they are labeled as weak and strong pain medicine. The patient is told to use weak medicine as much as possible but to use the strong medicine if needed. These and other procedures may be used to decrease narcotic intake, delay the development of tolerance, and simultaneously give the patient superior relief of pain. Such methods require considerable care in selecting suitable patients but may greatly help both patient and physician.

In conclusion we wish to re-emphasize that this discussion is based only on the use of analgesics in the control of pain. These agents have many disadvantages and should be considered only when other therapeutic measures are not available. This is particularly true with respect to the chronic use of these drugs, in which situation the analgesics should be considered only as a last resort.

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Hypotension-inducing Drugs and Their Relation to Hypertension

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It is unfortunate that the term "hypertension" has come to be synonymous with increased blood pressure. This has led many to consider all deviations of blood pressure above normal as evidence of hypertensive disease and to place undue and unjustified emphasis on the level of the blood pressure as the fundamental disturbance in this common disorder. This erroneous concept has resulted in the idea that any drug that lowers blood pressure, regardless of the mechanism of its action, is a potential therapeutic agent in hypertensive disease; whereas any disturbance that tends to elevate the blood pressure probably is a factor in the pathogenesis of the disease.[1] Much of the enthusiasm attending the introduction of hypotensive agents in the treatment of hypertensive disease is the result of these misconceptions.

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Significance of Elevation in Blood Pressure

The arterial blood pressure depends on the force of the heart beat, the elasticity of the arterial tree, and the peripheral resistance. Systolic pressure reflects primarily the force of cardiac contraction, i.e., the cardiac output, and the elasticity of the arterial system. Central resistance is conditioned primarily by the elasticity of the aortic wall and the capacity of the aorta, which determine the resistance to blood flow during systole. Rigidity of the aortic wall such as occurs in atherosclerosis increases the resistance and decreases the capacity of the aorta. The consequence of these changes is an increase in central resistance to blood flow which results in an increase in systolic pressure. Elevation in systolic pressure, therefore, is observed most commonly in generalized arteriosclerosis.[2]

Hypertensive disease, on the other hand, is characterized by elevation in diastolic pressure

secondary to increased peripheral resistance related to the caliber of the smaller arterioles and capillaries and to a lesser extent to the caliber of the venules. Normally, nervous and local hormonal factors as well as the inherent tone of the blood vessels regulate this peripheral resistance; it is an alteration in this peripheral resistance which constitutes the fundamental deviation observed in hypertensive disease. Diastolic pressure also depends to some extent on the heart rate and tends to fall as duration of diastole is lengthened.

Another hemodynamic feature of hypertensive disease is that the cardiac output, despite the elevated blood pressure, remains normal. Any mechanism that reduces the blood pressure by reducing cardiac output would accordingly exert a potentially deleterious effect despite the lowering of the abnormally elevated blood pressure.[2]

Any rational consideration of the therapy of hypertension requires an appreciation of the significance of the elevation in blood pressure observed in a given patient as well as of the mechanism of action of the hypotensive drug used to lower the blood pressure.

Rationale of the Use of Hypotensive Drugs

In the rational use of any drug one attempts to counteract the pathogenic factors responsible for the disease under treatment or, if this is not possible, to alleviate the undesirable effects of the disturbance.[3] Hypotensive drugs do not attain the first of these goals, since they fail to remedy the fundamental disturbance in hypertension. One can at best hope to mitigate the effects of the elevated blood pressure, which, however, is only one hemodynamic manifestation of the basic disturbance. As yet there is no general agreement regarding the nature of the fundamental disturbance responsible for the development of hypertensive disease and no truly rational therapy is available for its management.

The only rationale for the use of hypotensive agents in hypertension is the generally accepted assumption that the elevation in blood pressure per se exerts a deleterious effect on the organism, and hence any procedure that lowers the blood pressure, regardless of whether or not it affects the basic mechanism responsible for the elevation, is desirable. This is particularly true in the accelerated (or malignant) phase of the disease, which is characterized by an inordinate rise in blood pressure. It is in this stage of the disease that hypotensive drugs have proved of greatest value. Their apparent benefit in management of advanced hypertensive disease and their capacity to reverse the accelerated (malignant) phase of the disorder to the more benign stage are evidence that the excessive elevation in blood pressure contributes to the fatal outcome. In the more moderate elevations in blood pressure as seen in the benign stage of the disease, however, lowering of the pressure by nonspecific methods is of questionable value. One might assume that such a lowering would lessen the work of the heart and hence reduce the possibility of cardiac failure, which complicates two-thirds of the cases of hypertension. This would be desirable were it not for the fact that lowering the pressure with the available drugs may also reduce the blood flow through certain vital organs as well as induce other undesirable side effects.[3]

The available hypotensive drugs do not affect the primary disturbance responsible for the rise in blood pressure and its consequences; they alter the tone of the vascular smooth muscle by action directly or indirectly on structures remote from this muscle, namely, the autonomic ganglia, the chemoreceptors, baroreceptors and mechanoreceptors of the circulation, and the central nervous system.[3] Such drugs as the nitrites and thiocyanate, which act directly on receptors in the blood vessels, are no longer used in hypertension.

Drugs Used in Hypertensive Disease

The level of the blood pressure, although variable and not a criterion of the severity of disease, is the most readily available measure of the degree of hypertension in a given patient. Clinicians for many years have been preoccupied, therefore, with attempts to lower blood pressure by the use of hypotensive drugs. During the early decades of this cen-

TABLE 1

SOME HYPOTENSIVE AGENTS USED IN TREATMENT OF HYPERTENSION

GENERIC NAMES	TRADE NAMES
Drugs acting on the central nervous system:	
Hydralazine hydrochloride*	APRESOLINE®
Rauwolfia serpentina	RAUDIXIN® RAUSERPA®
Reserpine	RAULOYDIN® RAURINE® RESERPINE® RESERPOID® ROXINOID® SANDRIL® SERPASIL® SERPILOID®
Rescinnamine	MODERIL®
Ganglionic blocking agents:	
Chlorisondamine chloride	ECOLID®
Hexamethonium chloride	BISTRIUM® ESOMID® HEXAMETON® HIOHEX® METHIUM®
Mecamylamine hydrochloride	INVERSINE®
Pentolinium tartrate	ANSOLYSEN®
Veratrum derivatives:	
Alkavervir	VERILOID®
Cryptenamine acetates and tartrates	UNITENSEN®
Protoveratrines A and B	VERALBA®
Protoveratrine maleates	PROVELL MALEATE®

*Also exerts a moderate degree of adrenergic blocking action.

tury, nitrites and nitrates were utilized because of their capacity to relax smooth muscle. Subsequently thiocyanate was recommended, and from time to time other hypotensive agents such as tetraethylammonium chloride, pyrogenic extracts and other similar hypotensive drugs had an evanescent vogue. The serious side effects these agents induced and their relative ineffectiveness soon led to their abandonment. During recent years the discovery of more effective and less toxic hypotensive drugs has renewed interest in this field.

Table 1 lists the hypotensive drugs most commonly used in treatment of hypertension. We may classify them, as shown in the table, into three major groups: (1) those acting on the central nervous system, particularly on the midbrain and reticular formation, (2) those acting on autonomic ganglia, and (3) the Veratrum derivatives which act on the baroreceptors. In addition, phenoxybenzamine, a sympatholytic drug, has been tried; however, because of its serious side effects it is not used alone but is available in combination with *Rauwolfia* and protoveratrine (MIO-PRESSIN®). Because emotional disturbances elevate blood pressure, sedatives such as phenobarbital are also often of value for their incidental effects on the level of blood pressure.

The most widely used hypotensive agents are preparations of *Rauwolfia serpentina* and its crystalline alkaloids reserpine and rescinnamine.[4] They have attained wide popularity because of their relative lack of acute toxicity. However, when used for long periods they may give rise to serious disturbances, and their hypotensive effect, except when used in excessive doses, is not directed primarily on the circulatory system but is a consequence of their tranquilizing effects.[3] The *Rauwolfia* alkaloids act primarily by inhibiting cerebral sympathetic centers in the hypothalamus and reticular formation. Their action on the circulatory system is relatively feeble when therapeutic doses are given, and many consider their hypotensive action under these conditions almost entirely a consequence of their tranquilizing action. This would account for their apparent ineffectiveness in patients in whom such tranquilization is not produced or in whom troublesome side effects appear. The latter include nasal stuffiness, lassitude, apathy, mental depression, impotence, loss of libido, hypermotility of the bowel, diarrhea and fibrositis.[3]

Hydralazine also acts centrally, but it induces weak adrenergic and peripheral actions as well. Its reputed action in neutralizing pressor agents is doubtful, since the existence of such agents in the circulating blood of the hypertensive patient is questionable.[1] The chief virtue of hydralazine is its capacity to dilate renal vessels. Headache, dizziness, tachycardia and a rheumatic febrile disturbance accompanied by tissue changes resembling those in collagen disease are its chief side effects.[3]

The autonomic blocking agents are the most

potent of the available hypotensive drugs. They act by interrupting vasomotor impulses normally transmitted through the autonomic ganglia. However, since this blockade also interrupts the transmission of other sympathetic and parasympathetic impulses, they induce such disturbances as blurred vision, constipation, ileus, urinary retention and impotence.[5] The reflex adjustment of the blood pressure to postural change is mediated through the autonomic ganglia, and hence postural hypotension is present whenever the drugs are used in adequate doses, and it may give rise to serious side effects.

The Veratrum derivatives are derived from *Veratrum viride,* a plant indigenous to wet areas along mountain streams of the Eastern and parts of the Midwestern states. In addition to preparations of the crude drug, crystalline preparations of mixed alkaloids (cryptenamine and protoveratrine) are available. A serious drawback to use of such mixtures is the fact that different alkaloids elicit unequal responses, as has been demonstrated, for example, for protoveratrine A and B. Hence when the proportion of the different alkaloids varies a variable response is inevitable.

Veratridine and protoveratrine act on the receptors in the coronary arteries through afferent pathways in the vagus. Protoveratrine and alkavervir act on the carotid sinus and carotid body through the afferent fibers of the glossopharyngeal nerve.[6] The drugs interrupt the incoming or central impulses which normally impinge on the medullary vasomotor center and thus induce a hypotensive and bradycardic action. Their most serious side effects are epigastric burning, nausea, vomiting, salivation and a choking sensation, and there is only a narrow margin between the effective hypotensive dose and the toxic dose.

Drastic restriction of sodium effects a marked lowering of blood pressure in many hypertensive patients,[1,2,7] but it is often difficult to apply to the degree necessary to elicit this effect. Attempts have therefore been made to facilitate this action by administering a mercurial diuretic simultaneously. More recently, claims of striking effects have been made for the use of a nonmercurial diuretic, chlorothiazide, in combination usually with preparations of *Rauwolfia* or other hypotensive agents. Simultaneous sodium restriction also enhances the effect of the hypotensive drugs, and it is not unexpected, therefore, that a similar response should follow the induction of sodium loss by so potent a natruretic agent as chlorothiazide. Further careful studies of the effect of sodium restriction alone as compared with that of the newer diuretics are necessary before the place of the latter in treatment of hypertensive disease is clarified. In spite of claims to the contrary, there is no evidence that chlorothiazide exerts any hypotensive action except that secondary to its natruretic effect.

Side Effects

In addition to the specific side effects already described, the most serious drawback to use of any depressor agent in hypertension is the effect of lowering the blood pressure on the blood flow through such vital organs as the brain, heart and kidney. Various hypotensive drugs differ in this respect.[7] Unfortunately, in seriously ill patients the effect of these drugs may often lead to such deterioration of cardiac and renal function as to harm rather than benefit the patient by the drop in blood pressure. Whereas patients with slight to moderate vascular impairment may be able to tolerate a reduction in blood pressure, this is not always the case in those with cerebral or coronary atherosclerosis or manifesting renal impairment, who are in most need of drastic therapy insofar as the hypertensive disease is concerned.[7]

The tendency of the available hypotensive drugs to induce undesirable side effects has led to the use of combinations of several of the drugs. Although such combinations may minimize the appearance of undesirable side effects,[8] it is questionable to what degree the hypotensive action of each constituent is manifested when agents acting by such diverse mechanisms are used in subeffective amounts.

Status of Hypotensive Therapy

The extensive clinical literature on the various hypotensive agents in use at present for

treatment of hypertension is conflicting. Reports of their efficacy in lowering blood pressure in ambulatory patients vary from claims of reduction to normal levels to little or no response unless intolerable doses are given, with undesirable side effects. Unfortunately most of the published studies are poorly controlled.[7] The level of blood pressure is subject to spontaneous fluctuations, and one must take into account the doctor-patient relationship, the powerful effects of a reassuring and enthusiastic approach to the patient, and the effects of hospitalization and other measures used to alleviate situational stresses; all these factors profoundly affect blood pressure. Such nonspecific factors are undoubtedly responsible for some of the more enthusiastic reports regarding the efficacy of these drugs in lowering blood pressure.

There is good evidence, however, to indicate that these agents are of undoubted value in patients with the severe, progressive accelerated stage of the disease designated as the malignant phase and possibly in hypertensive encephalopathy.[7] In such cases the use of the drugs has permitted a reversal of such objective manifestations as retinopathy and cardiac enlargement and induced a remission to the more benign phase of the disease. Approximately one-third to one-half of the patients observed in this stage of the disease may be benefited temporarily and their lives prolonged over the survival period observed prior to introduction of hypotensive drugs. Most of the available drugs are efficient for this purpose if used with careful adjustment of dosage and attention to precipitous drops in blood pressure and deterioration of renal function. The status of the cardiac and renal function determines the drug which is to be administered in a given case.

Most observers agree that the use of potent hypotensive agents is not indicated in the asymptomatic benign phase of hypertensive disease, since the potential harm outweighs the benefit to be derived by empirical lowering of the blood pressure. For these patients the administration of such agents as the *Rauwolfia* alkaloids is indicated, for their tranquilizing rather than their hypotensive effect, although in most cases simple reassurance or the use of a mild sedative may at times give equally good effects with less danger of troublesome side effects.

Conclusion

The hypotensive agents now used in hypertensive disease obviously are still inadequate, and a much more basic approach to the problem is needed before a satisfactory treatment will be available. Until drugs exerting a more specific hypotensive action and devoid of the serious side effects induced by those used at present become available, treatment must remain symptomatic and limited to the more advanced stages of the disease and its complications. The greatest value of the presently available hypotensive drugs is in the management of the accelerated (malignant) stage of the disease; their use in such cases has materially improved the immediate prognosis. As more specific hypotensive agents become available, the range of applicability of drug therapy in hypertension will enlarge. However, not until it is possible to counteract the basic derangement responsible for the elevation in blood pressure can any therapy be considered truly rational.

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Adrenergic Drugs and Their Antagonists

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THE term "adrenergic" was originally proposed by Dale[1] as part of a physiologic classification of nerves. He used it to designate nerves (most of those in the anatomic sympathetic system) which produce their effects by the release of a substance similar to epinephrine (now known to be predominantly norepinephrine). The term has proved to be very useful and has been extended, not entirely justifiably, to designate responses to the activity of these nerves, drugs which produce similar effects, drugs which block responses to adrenergic nerve activity or to adrenergic stimulants, and so on. Adrenergic responses may be increased or decreased by drugs which act through a variety of mechanisms including reflex and central, but the present discussion will be limited to those that act directly on the responding or effector cells, the sympathomimetics and adrenergic blocking agents.

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Sympathomimetic Amines

Actions of the sympathomimetic amines can be classified as (1) central nervous system stimulant, (2) peripheral stimulant and depressant, (3) cardiac stimulant and (4) metabolic. This short survey cannot deal exhaustively with any of these, and the interested reader should consult more comprehensive reviews[2-4] for details of the actions of this important group of drugs.

Most sympathomimetics have only limited selectivity in their actions on various organ

systems. All useful sympathomimetics can be demonstrated to have all the actions listed, although their relative potencies with respect to the various facets of action vary widely. *Most clinical "side effects" are essential parts of the pharmacologic action which may be desired in other patients and circumstances.* Thus cardiac stimulation is the desired effect when isoproterenol (ALUDRINE®, ISUPREL®, NORISODRINE®)* is administered to a patient with heart-block, but it is an annoying side effect when the same drug is used in the treatment of asthma. Similarly, stimulation of the central nervous system is the desired action of methamphetamine (DESOXYEPHEDRINE®, DESOXYN®, METHEDRINE®) when employed to combat the sedative action of other drugs, but is an undesirable side effect when the drug is used to elevate the blood pressure during spinal anesthesia. The sympathomimetics are frequently employed locally to minimize undesired actions elsewhere in the body.

Central nervous system actions—One of the most common uses of sympathomimetic amines is to produce central nervous system stimulation. This application is important enough to warrant an entire review, but a simple list of the most important specific applications must suffice here. They are: to delay fatigue, to decrease appetite, to stimulate respiration, to elevate mood in depressed mental states, to increase attention span in children with behavioral difficulties, and to combat the sedative effects of other pharmacologic agents. The first two applications are most commonly abused, and the use of sympathomimetic amines for these purposes should be carefully supervised by a physician.

Peripheral actions—This category includes actions of the sympathomimetics on smooth muscle and exocrine glands, of which the former are by far the more important. All of them are prominent components of the action of epinephrine (ADRENALIN®, SUPRARENIN®). Consequently the net effects of this drug are often the resultant of essentially opposite actions. Cardiac stimulation and vasoconstriction, especially of skin vessels, tend to raise the blood pressure, while dilatation of blood vessels in skeletal muscle may minimize this rise or result in a fall in diastolic pressure and total peripheral resistance. Tachycardia represents the direct action of epinephrine on the heart, but bradycardia may result from vagal discharge reflexly induced by the rise in systolic pressure. Peripheral depressant (inhibitory) effects include dilatation of bronchi and decreased tone and motility of the intestines and possibly of the ureters and gallbladder.

A tremendous number of sympathomimetic amines have been tested in a continuing effort to obtain improved specificity of action.[3] The success of these efforts has been considerable but far from complete, as may be seen in table 1. Administration of a predominantly stimulant (excitatory) agent will increase systolic and diastolic pressures and total peripheral resistance. Effects on local blood flows vary in different organs depending on the balance between vasoconstriction in a particular vascular bed and the increased perfusion pressure.[5,6] Of particular importance is the fact that renal blood flow is usually decreased.[7] Pressor agents having limited cardiac action invariably cause reflex bradycardia. In contrast, some agents with predominantly depressant actions (e.g., isoproterenol) exert important cardiac effects which summate with the reflex response to the hypotension to produce a severe tachycardia.

Cardiac stimulant actions—The rate and force of contraction of the myocardium are increased markedly by many sympathomimetics. Induction of cardiac arrhythmias is a possible although not a common occurrence except in the presence of myocardial sensitization by agents such as cyclopropane or chloroform. Palpitation usually is due to increased strength or rate of the heart action, or

*Selection of a name by which to designate a specific drug presents very real problems. The official or generic name is the logical choice because it clearly designates the active agent irrespective of its source or commercial encumbrances. However, generic names are lost to many physicians in the deluge of trade-name advertising. Use of trade names alone is obviously impossible because 10 or more may apply to a single compound with equal validity. In this paper, generic names are used throughout. One or more trade names for each drug have been added in table 2 and the first time the agent is mentioned in the text.

TABLE 1

ACTIONS OF SYMPATHOMIMETIC AMINES

DRUG	RELATIVE ACTIVITIES*			
	Central Nervous System Actions	*Peripheral Excitatory Actions*	*Peripheral Inhibitory Actions*	*Cardiac Actions*
Epinephrine	+++	++++	+++	++++
Norepinephrine	++	++++	+	++++
Amphetamine	++++	++	+	++
Methamphetamine	++++	++	+	++
Ephedrine	+++	++	++	+++
Phenylpropanolamine	++	++	++	++
Hydroxyamphetamine	±	+++	+	++
Mephentermine	+	+++	±	++
Methoxamine	−	+++	±	−
Phenylephrine	+	+++	++	±
Metaraminol	++	+++	±	++
Phenmetrazine	++	++	±	+
Cyclopentamine	±	+++	±	+
Propylhexedrine	±	+++	±	+
Tuaminoheptane	−	+++	++	+++
Naphazoline	Depressant	+++	−	−
Tetrahydrozoline	Depressant	+++	−	−
Isoproterenol	++	−	++++	++++
Methoxyphenamine	+ or depressant	+	++	?
Nylidrin	+	−	+++	++

*Any simplified classification must be somewhat arbitrary. We have tried to present the relative magnitude of the various actions of the agents listed. The designations are not in terms of absolute potency, which may be evaluated from the approximate doses listed in table 2.

both, rather than to arrhythmias. Methoxamine (VASOXYL®), phenylephrine (ISOPHRIN®, NEO-SYNEPHRINE®) and naphazoline (PRIVINE®) produce the least cardiac stimulation.[8] The cardiac actions of the sympathomimetic amines are usually considered side effects and are only rarely therapeutically useful. Ephedrine and isoproterenol are used to stimulate the automaticity of the myocardium in syncope due to complete heart-block or to carotid sinus hypersensitivity, but the results are often disappointing. Ephedrine is preferable for chronic treatment; isoproterenol has a much more rapid and powerful action and may be useful in emergencies. The use of sympathomimetics to restart the heart beat in the dying patient is rarely rewarding. The stimulant does not reach the heart after intravenous injection, and although direct injection into the ventricle may be effective temporarily, the response can be attributed largely to mechanical stimulation by the needle puncture.

Metabolic actions—These are major pharmacologic actions only in the case of epinephrine, although several other compounds have been demonstrated to possess them to a lesser degree. Epinephrine causes release of glucose from the liver, inducing glycogenolysis by activating liver phosphorylase. This is of great physiologic importance in maintaining the blood sugar level. Stimulation of glycogenolysis in muscle results in lactacidemia. The metabolic action of epinephrine is of therapeutic importance only in the emergency

TABLE 2

USES OF THE MORE COMMON SYMPATHOMIMETIC AMINES*

DRUG	COMMON TRADE NAMES†	APPROXIMATE DOSE‡ (MILLIGRAMS)	DURATION OF ACTION	VASO-CONSTRICTOR	BRONCHO-DILATOR	C.N.S. STIMULANT AND APPETITE SUPPRESSANT	MYDRIATIC	GENERAL ANTIALLERGIC
Epinephrine	Adrenalin§ Suprarenin§ (Others)	0.5 I.M.	Very short	Yes**	Yes	No	No	Yes
Norepinephrine Levarterenol§	Levophed§	0.004 per minute I.V.	Very short	Yes	No	No	No	No
Amphetamine	Benzedrine (Others)	5-10 P.O.	Long	Yes**	No	Yes	Yes	No
Dextro-amphetamine‖	DEXEDRINE®‖ (Others)	5 P.O.	Long	Yes**	No	Yes	Yes	No
Methamphetamine	Desoxyephedrine Desoxyn Methedrine (Others)	2.5-5 P.O. 10-20 I.M.	Long	Yes	No	Yes	No	No
Ephedrine	(Many)	25-50 P.O. or I.M.	Long	Yes	Yes	Yes	Yes	No
Phenylpropanolamine	PROPADRINE®	25-50 P.O.	Short	Yes	Yes	Yes	No	No
Hydroxyamphetamine	PAREDRINE®	10-20 I.M. 5-10 I.V.	Short	Yes	No	No	Yes	No
Mephentermine	Wyamine	15-45 I.M. 15 I.V.	Long	Yes	No	No	No	No
Methoxamine	Vasoxyl	10-15 I.M. 5 I.V.	Long	Yes	No	No	No	No
Phenylephrine	Isophrin Neo-Synephrine	20-50 P.O. 5 I.M. 0.5 I.V.	Short	Yes	Yes	No	Yes	No
Metaraminol	Aramine	2-10 I.M. 0.5 I.V.	Long	Yes	No	No	No	No
Phenmetrazine	PRELUDIN®	25-50 P.O.	Long	No	No	Yes	No	No
Cyclopentamine	CLOPANE®	25 I.M.	Short	Yes	No	No	No	No
Propylhexedrine	Benzedrex		Short	Yes**	No	No	No	No
Tuaminoheptane	Tuamine		Short	Yes**	No	No	No	No
Naphazoline	Privine		Short	Yes**	No	No	No	No
Tetrahydrozoline	Tyzine		Short	Yes**	No	No	No	No
Isoproterenol	Aludrine Isuprel Norisodrine	5-10 sublingually	Very short	No	Yes	No	No	No
Methoxyphenamine	Orthoxine	50-100 P.O.	Long	No	Yes	No	No	No
Nylidrin	ARLIDIN®	6 P.O.	Long	Vasodilator	No	No	No	No

*Entries cover only the *major* uses of an agent and are made on the basis of published clinical reports. They are not necessarily recommendations.

†Not more than three of an often large number of trade names are given. Drugs dispensed under other trade names can be correlated with the table on the basis of the generic names which are included on the labels.

‡Doses are given as a rough measure of relative potency and vary with the intended effect. Concentrations for local use are not included.

§l-Isomer. ‖d-Isomer.

**Employed locally; other vasoconstrictors are used both locally and systemically.

treatment of severe insulin reactions when glucose is not immediately available. The success of this procedure depends on adequate stores of liver glycogen.

Clinical Applications of Sympathomimetics

A full discussion of the clinical applications of the sympathomimetic amines is impossible in this limited space. We shall, instead, single out a few common clinical problems and point out the role of sympathomimetics in their management (table 2).

Acute allergic reactions—It is probably fair to state that we know as little about the mechanisms by which epinephrine provides its excellent symptomatic relief of urticaria, acute serum reactions, angioneurotic edema, etc. as we do about the basic mechanisms of their induction. Both subjective (itching, etc.) and objective manifestations are benefited. It is highly probable that vasoconstriction plays a role in this effect of epinephrine, but other factors are involved as the relief is more complete than with other vasoconstrictors. The response to epinephrine is more rapid and complete than that to the antihistaminic drugs. The two types of agents are commonly employed together to take advantage of the more prolonged action of the latter. Epinephrine is much less effective in subacute or chronic than in acute allergic reactions.

Bronchodilatation—The first consideration in the treatment of dyspnea should be etiology. The sympathomimetic amines are contraindicated in the treatment of dyspnea due to myocardial failure. However, the powerful bronchodilator action of amines with peripheral inhibitory properties is an important therapeutic tool in the management of bronchial asthma. In the treatment of an acute attack, a potent, rapidly acting drug such as epinephrine or isoproterenol is desirable. The former may be injected intramuscularly or given by inhalation. The latter should not be injected because of its potent cardiac effects but can be administered by aerosol or sublingually, most commonly and effectively by the former route.

The development of "epinephrine fastness" in some asthmatic patients receiving large amounts of the drug is a well-established phenomenon. There is less evidence for the development of tolerance to isoproterenol, but this may be due in part to inadequate observations. Fastness usually develops as a result of misuse, particularly too frequent administration, and patients should be warned regarding this possibility as well as the usual cardiovascular and central effects of overzealous self-medication. Weaker but longer-acting agents such as ephedrine or methoxyphenamine (ORTHOXINE®) may be used prophylactically or to abort milder attacks. Ephedrine is used most frequently, and is usually combined with a xanthine derivative such as aminophylline and with a barbiturate to control central stimulation. Many cases of chronic emphysema have a considerable element of bronchospasm, and judicious use of aerosolized sympathomimetic bronchodilators may contribute materially to their management.

Vasoconstriction—Local vasoconstriction represents one of the most common and valid uses of the sympathomimetic amines. Their use to delay absorption of another drug such as a local anesthetic is well established. Epinephrine appears to be the most effective agent for this purpose, although many others have been employed with satisfactory results. Hundreds of pounds of sympathomimetic amines, in almost every conceivable pharmaceutical base, are applied annually to the mucous membranes of the nose to control rhinorrhea. Almost any agent with a strong vasoconstrictor action is effective when applied in solutions of suitable concentration, as are the volatile bases of some of the sympathomimetic amines. The choice of agent depends primarily on the incidence and severity of side effects. Central nervous system stimulation is perhaps the most commonly encountered side effect, but cardiac and pressor responses to absorbed drugs may also represent contraindications in individual patients. Sympathomimetic amines not having the phenethylamine structure such as tuaminoheptane (TUAMINE®) and propylhexedrine (BENZEDREX®) do not produce any central nervous system stimulation. Imidazolines, naphazoline (Privine) and tetrahydrozoline (TYZINE®) produce central depression,

an effect seen particularly in children and usually associated with considerable hypothermia. Severe coma from this central depression has been reported, and it is probably best not to use these agents in children. Chronic administration of any of the nasal decongestants can result in what appears to be a paradoxical vasodilation, iatrogenic rhinorrhea. This is primarily due to a reactive hyperemia secondary to prolonged drug-induced vasoconstriction and mucosal ischemia. Reapplication of a constrictor provides only temporary relief and perpetuates the condition. Only discontinuation of vasoconstrictor therapy can interrupt this vicious circle.

The use of sympathomimetic agents to raise the blood pressure in hypotensive states depends primarily on their vasoconstrictor action, although cardiac stimulation may play some role in the case of agents with a strong cardiac action (table 1). Ephedrine, mephentermine (WYAMINE®), metaraminol (ARAMINE®), methamphetamine (Desoxyephedrine, Desoxyn, Methedrine and many others), methoxamine (Vasoxyl), norepinephrine (LEVOPHED®) and phenylephrine (Isophrin, Neo-Synephrine) are all recommended to maintain a normal blood pressure during spinal anesthesia. Hypotension during spinal anesthesia is due to interruption of sympathetic vasoconstrictor tone to and pooling of blood in the anesthetized area. Tachycardia and vasoconstriction in areas above the level of anesthesia are reflex responses to the hypotension and contribute greatly to the patient's discomfort and apprehension. Administration of a pressor agent helps to balance the level of constriction by increasing vascular tone in "denervated" areas and thus reflexly decreasing sympathetic tone in other regions. This use of sympathomimetic agents should be considered as a contribution to the subjective welfare of the patient and not as protection against shock. The available agents differ primarily in their duration of action; phenylephrine and particularly norepinephrine are short-acting, whereas methoxamine is probably the longest-acting member of the group listed.

In "shock," a vascular condition much easier to talk about than to define, the physiologic lesion is vasoconstriction rather than vasodilatation, as evidenced by cold, clammy skin and slow vascular filling. Considerable evidence is accumulating to show that the essential determinant of irreversible shock is inadequate tissue blood flow.[9] Sympathomimetic amines administered to raise the blood pressure may increase vasoconstriction sufficiently to cause a further decrease in blood flow. Administration of vasoconstrictor agents in shock is especially to be deplored in the not infrequent cases in which it masks the need for the administration of additional blood or other fluid and electrolyte therapy.

Adrenergic Blocking Agents

Agents which specifically block responses to adrenergic nerve activity or to circulating sympathomimetics are a relatively new introduction into medicine. This type of action has been variously referred to as adrenolytic or sympatholytic, but these terms are inaccurate. All agents in this group block responses to both circulating agents and nerve activity. The former are always blocked more readily, but the differential varies widely, being greatest for certain of the benzodioxans. The term "sympatholytic" has lost its usefulness because it has been employed frequently to refer to any action—reflex, central, ganglionic, etc.—which decreases the sympathetic nerve activity.

One may generalize that all adrenergic blocking agents have a similar spectrum of activity with respect to the various adrenergic actions outlined in the previous section. Peripheral excitatory responses, such as vasoconstriction, and cardiac arrhythmias are effectively blocked. The peripheral inhibitory responses and the chronotropic (rate) and inotropic (force of myocardial contraction) responses of the heart are unaffected. Metabolic and central nervous system responses are variably and usually ineffectually inhibited.

Although all the clinically available adrenergic blocking agents produce a similar pattern of blockade, its completeness varies considerably, largely because of side effects which limit the tolerated dosage of the various

agents. Four general groups may be recognized on the basis of the maximal blockade to be obtained in patients: (1) relatively complete blockade for long periods—phenoxybenzamine (DIBENZYLINE®); (2) significant but partial and usually transient blockade—phentolamine (REGITINE®), tolazoline (PRISCOLINE®), azapetine (ILIDAR®); (3) partial blockade, only for short periods—piperoxan (BENODAINE®); (4) never significant blockade in man—ergot alkaloids. Details of the pharmacology of these drugs have been comprehensively reviewed[10] and will not be repeated here.

Phenoxybenzamine (Dibenzyline)—This is the most powerful and effective of the adrenergic blocking agents available for clinical use. Its basic pharmacology is the same as that of Dibenamine, except that phenoxybenzamine possesses considerable antihistaminic activity and is five to eight times more potent. The incidence and severity of side effects are much less than with Dibenamine. The blockade produced develops relatively slowly over a period of one-half to one hour even after intravenous administration. A major part of the blockade persists for 24 hours, and significant amounts for several days. Phenoxybenzamine is the only clinically available agent capable of producing relatively complete adrenergic blockade in man in tolerated doses. Side effects include local irritation if the drug is injected into solid tissues, nasal stuffiness, tachycardia and sometimes a subjective lethargy and weakness which has not been adequately explained. Gastrointestinal upsets are not common but may occur with large oral doses. Postural hypotension and dizziness, to which patients compensate after variable periods, reflect the desired blockade of sympathetic vasoconstriction. The drug may be administered by intravenous infusion over a period of one-half to one hour, or orally, but is several times more effective by the former route.

Tolazoline (Priscoline) and phentolamine (Regitine)—These agents produce moderately effective blockade in doses which are tolerated for short periods, but have many other pharmacologic actions including sympathomimetic (tachycardia, palpitation, occasionally arrhythmias), parasympathomimetic (increased gastrointestinal motility, cramping, diarrhea), histaminelike (stimulation of gastric acid secretion), and a direct peripheral vasodilatation unrelated to adrenergic blockade. This direct vasodilatation is induced by lower doses than those required to produce significant blockade. The histaminelike action of tolazoline is sufficiently important for this agent to be used as an effective substitute for histamine in tests of gastric secretory ability.[11] This action also may produce gastric distress and peptic ulceration in patients on chronic medication with this agent. Phentolamine is the more effective adrenergic blocking agent, and the other actions listed are relatively less prominent than with tolazoline. Both drugs may be administered parenterally or orally but are much less effective by the latter route. It appears probable that little or no adrenergic blockade is produced by tolazoline in oral doses of 25 to 50 mg. three or four times a day. The duration of action of these agents appears to be too short to justify intra-arterial injection.

Azapetine (Ilidar)—Although quite different in structure, azapetine produces essentially the same adrenergic blockade and peripheral vasodilatation as does tolazoline. It may have a somewhat lower incidence of side effects, particularly those related to the gastrointestinal tract. The drug is usually administered orally.

Piperoxan (Benodaine, 933F)—Piperoxan is the only member of the extensive series of benzodioxans which is employed clinically in North America, and its use is restricted entirely to short periods of intravenous administration in the diagnosis of pheochromocytoma. It is much more effective in blocking responses to circulating sympathomimetics than those to sympathetic nerve activity, and the latter are not affected by tolerated doses in man. A combination of direct peripheral vasoconstriction and a centrally mediated increase in vasomotor activity usually produces a rise in blood pressure in normal persons and in patients with essential hypertension. Even during carefully controlled infusions, side effects are common and not infrequently severe. These in-

clude a sharp rise in blood pressure, dizziness, palpitation and precordial distress.

Ergot alkaloids—Although certain partially hydrogenated ergot alkaloids (HYDERGINE®) are among the most potent adrenergic blocking agents known, other effects, particularly a central action producing nausea and vomiting, are sufficiently prominent to preclude the administration of doses adequate to produce clinically significant adrenergic blockade. Such peripheral vasodilatation and decrease in blood pressure as these agents produce in patients can be attributed to a central action. Although hydrogenation decreases the peripheral smooth muscle stimulant action of the ergot alkaloids, it is not eliminated. Hydergine produces significant uterine stimulation and direct peripheral vasoconstriction, readily demonstrated in denervated extremities. These effects are considerably more prominent components of the action of dihydroergotamine (DHE45). The clinical usefulness of dihydroergotamine and of the natural alkaloids, such as ergotamine, is limited to smooth muscle stimulation in obstetrics and in the treatment of migraine.

Clinical Applications of Adrenergic Blocking Agents

Effective adrenergic blocking agents have only recently been introduced into clinical medicine, and their ultimate place in the management of various clinical problems is yet to be determined. Unfortunately, many therapeutic studies with these agents have failed to indicate the degree of adrenergic blockade produced. This deficiency makes it difficult to determine whether failures were due to inadequate dosage or to the fact that the condition in question was not amenable to this type of therapy and, similarly, whether favorable results were due to adrenergic blockade per se or to other actions of the drugs administered.

Pheochromocytoma—The most firmly established uses of adrenergic blocking agents are in the diagnosis and management of pheochromocytoma.[12] Tests with these agents are not valid unless the patient's blood pressure is elevated at the time of administration, and even when applied with care, no single test is entirely reliable. Phentolamine is generally accepted as the most useful agent for preliminary screening and may be administered as an office procedure. The standard test dose has been selected to minimize false negative responses, although these are not unknown. This leads to a very considerable number of false positives, as high as 10 to 15 per cent in some studies. A dose of 5 mg. is administered rapidly intravenously and a fall in blood pressure of 35/25 mm. Hg or greater is considered to be a positive result.[13] This does not provide a definitive diagnosis, and all patients showing a positive response should be subjected to further study.

Piperoxan provides a somewhat more precise test, but serious reactions are not uncommon and it is best carried out in hospital. A dose of 0.25 mg. per kilogram, not over 20 mg. total, is administered intravenously over a period of not less than two minutes, preferably into an infusion without the patient's knowledge. Most patients with essential hypertension respond with an increase in blood pressure, and any predominantly depressor response is considered positive. Both false positive and false negative responses occur. Uremia and sedation appear to increase the incidence of false positives.

Phenoxybenzamine effectively lowers the blood pressure of many patients with essential hypertension and thus does not provide a reliable test for pheochromocytoma when used alone. However, patients with functional adrenal medullary tumors are extremely sensitive to this agent and a profound fall in blood pressure in response to phenoxybenzamine is suggestive. The drug may be used to advantage in combination with histamine in patients who are seen during periods of normal or only moderately elevated blood pressure. A positive pressor response to the histamine test, converted to a depressor response by the prior intravenous administration of 1.0 mg. per kilogram of phenoxybenzamine, represents the most specific diagnostic test in this condition, with the exception of chemical determination of epinephrine and norepinephrine excretion. Considerably smaller doses of phenoxybenzamine usually suffice, but this dose

is well tolerated by bed patients and provides essentially complete blockade.

Phenoxybenzamine is the agent of choice for medical management of pheochromocytoma, although oral phentolamine is of some value if administered every three hours. Preoperative use of phenoxybenzamine may allow cardiac compensation and improvement in the general condition of poor-risk patients. Patients with functional metastases, those in whom the tumor is not located at operation, etc. can be controlled effectively for long periods by the oral administration of phenoxybenzamine, usually in a dose of 30 to 100 mg. daily. Tolerance does not appear to develop over periods of many months.

The role of adrenergic blocking agents during operation for pheochromocytoma is still controversial, but evidence is accumulating to indicate the desirability of blocking patients with phenoxybenzamine prior to and through the period of operation. This procedure allows the cardiovascular system to adjust to the absence of adrenergic vasoconstriction at a time when it is not also subjected to operative trauma, and effectively prevents serious pressor responses during operative manipulation of the tumor. Sympathomimetics such as norepinephrine do not effectively raise the blood pressure postoperatively in patients so treated, but the necessity and desirability of such pressor therapy can be seriously questioned. If the patient is not pretreated with an adrenergic blocking agent, some control of untoward pressor responses during operation can be obtained by the repeated intravenous administration of phentolamine.

Essential hypertension—Overactivity of the sympathetic nervous system probably is not a major factor in the etiology of essential hypertension, and treatment with adrenergic blocking agents can be considered only as symptomatic management. However, an agent such as phenoxybenzamine is capable of blocking vasomotor activity as effectively as a ganglionic blocking agent, and without side effects such as constipation which result from the concomitant unnecessary blockade of parasympathetic ganglia. The most important drawback to adrenergic blockade in the treatment of hypertension is tachycardia, which results from failure to block the cardiac component of the reflex response to the lowered blood pressure. This side effect may be considerably decreased by combining phenoxybenzamine with a *Rauwolfia* preparation, a procedure which also decreases the dose of the former required. Promising results in a high percentage of cases of moderate and severe hypertension treated with a mixture of phenoxybenzamine, *Rauwolfia* and protoveratrine (MIO-PRESSIN®) have been reported,[14] but it appears that the amount of phenoxybenzamine in this preparation is suboptimal. Daily oral doses of several hundred milligrams of phenoxybenzamine may be required even in combination with a *Rauwolfia* preparation, and may control some cases not amenable to other therapy. Patients tend to compensate for the postural hypotension associated with these larger doses of the drug when they are maintained on continuous and relatively uniform medication.

Peripheral vascular disease—Adrenergic blocking agents have been used extensively in the treatment of peripheral vascular disease. However, this is frequently without due consideration for the pathologic physiology involved or the pharmacology of the drugs employed. It is well known that blood flow in skeletal muscle is predominantly controlled by local factors which tend to produce maximal vasodilatation under conditions of ischemia and that vasomotor tone is of minor importance in this vascular bed. As would be expected on the basis of the physiologic control of muscle blood flow, adrenergic blocking agents, with or without a direct vasodilator action, are of little value in the treatment of intermittent claudication. It is of interest to note that there is a tendency to treat this condition with ineffectual oral doses of the weaker adrenergic blocking agents, with results which conform to the known variable course and subjective nature of the disease. Although it may not provide significant benefit, this procedure at least minimizes side effects.

In contrast to the muscle bed, blood vessels in the skin are predominantly under sympathetic vasomotor control and can be dilated

effectively by adrenergic blocking agents. Adequate doses of phenoxybenzamine have been shown to cause increases in hand and foot blood flow about 80 per cent as great as those produced by nerve block. This is essentially the maximal response obtainable with any systemically administered medication. Adrenergic blocking agents are indicated primarily in conditions involving inadequate skin blood flow and a significant component of sympathetically mediated vascular spasm.[15] Raynaud's disease fits these requirements particularly well, and attacks can be prevented effectively by several of the available agents. The dose should be adjusted to each patient to provide maximal relief with minimal side effects. Oral phenoxybenzamine is particularly effective, some patients responding to as little as 30 mg. daily. The response appears to be somewhat better in the upper than in the lower extremities. Oral tolazoline, phentolamine and azapetine also are effective in many cases, but administration must be more frequent and maximal tolerated doses may be required.

A significant vasospastic component appears to be involved also in many conditions precipitated by some other primary lesion such as atherosclerosis, acute arterial occlusion, etc., and here adrenergic blockade frequently produces considerable warming of the hands and feet and facilitates healing of skin lesions.[16] Muscle blood flow is rarely improved significantly. Nevertheless, benefit may be considerable because inadequate skin blood flow is usually the factor which actually compromises viability. It is important to administer the drugs in amounts sufficient to produce really significant blockade. In acute situations, phenoxybenzamine in doses up to 1.0 mg. per kilogram intravenously with the patient at bed rest, followed by oral administration, provides the most effective blockade. In more chronic ambulatory cases, oral administration may begin at 10 to 20 mg. three times a day and be increased gradually until the desired effect or the limit of tolerance is reached. Parenteral phentolamine, tolazoline or azapetine also may be of significant value but must be repeated at least every four hours for a sustained effect. Oral administration of these agents in the usual doses of 25 to 50 mg. three times a day is of limited value.

Glaucoma—Systemically administered Dibenamine has been shown to produce a dramatic reduction of elevated intraocular pressures even under those conditions (atropine overdosage) in which no miosis occurs. This is particularly striking in patients with acute congestive glaucoma. The effect is believed to be due primarily to inhibition of secretion of aqueous humor. Phenoxybenzamine has received only limited trial in glaucoma but appears to produce a comparable effect with the added advantage that its oral effectiveness may allow more prolonged administration than has been possible with Dibenamine.

Cardiac arrhythmias—Both Dibenamine and phenoxybenzamine very effectively prevent ventricular arrhythmias associated with the administration of cyclopropane or other anesthetic agents.[17] Such arrhythmias are not of major importance today because the introduction of effective muscle relaxants and other anesthetic supplements allows the use of lower concentrations of sensitizing agents. However, the adrenergic blocking agents should be kept in mind for cases particularly prone to develop these arrhythmias. Current information does not warrant the clinical use of adrenergic blocking agents in arrhythmias other than those associated with anesthetic sensitization.

Conclusion

Sympathomimetics and adrenergic blocking agents are useful and effective drugs if employed with intelligence, understanding and flexibility.

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MEETINGS and Postgraduate Courses

Society for Clinical and Experimental Hypnosis, Chicago: Annual meeting, October 29-31 at the Morrison Hotel. The Institute for Research in Hypnosis of the Long Island University Postgraduate School will present its annual workshop in clinical hypnosis, October 27-29. For further information, write to: Administrative Secretary, Society for Clinical and Experimental Hypnosis, 750 North Michigan Avenue, Chicago 11.

University of Minnesota, Minneapolis: Courses to be presented at the Center for Continuation Study, 1958:

Obstetrics for specialists, October 6-8
Dermatology for general physicians, October 23-25
Pediatric radiology for radiologists, November 3-8
Fractures for general physicians, November 17-19
Neurology and neurosurgery for general physicians, November 17-22
Physical medicine for specialists, November 20-22

For further information, write to: Director, Department of Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14.

University of Oklahoma School of Medicine, Oklahoma City: Oregon-Oklahoma specialty meeting for practicing physicians, October 3-4; second colloquy on advances in medicine, devoted to arthritis and related disorders, November 12-15. For further information, write to: Office of Postgraduate Education, University of Oklahoma Medical Center, 801 Northeast 13th Street, Oklahoma City 4.

University of Southern California School of Medicine, Los Angeles: Postgraduate courses to be presented in 1958-1959:

Bedside clinics and set clinics in internal medicine, October 2-January 15
Therapeutic interviewing of patients with emotional problems, October 15-January 8
Advances in diagnosis and treatment of the last five years, October 16-17
Symposium on sexual problems seen in general practice, November 7
Workshops in water and electrolyte balance, January 16-18

For further information, write to: Director, Postgraduate Division, School of Medicine, University of Southern California, 2025 Zonal Avenue, Los Angeles 33.

University of Texas Southwestern Medical School, Dallas: Postgraduate courses to be presented in 1958-1959:

Ear, nose and throat, October 3-4
Orthopedic surgery, October 30-November 1
Psychiatry, November 3-5
Pulmonary diseases (Mattson seminar), May 22-23
The stomach and bowel, June 25-27

For further information, write to: Dr. John S. Chapman, Assistant Dean, Postgraduate Education, 5323 Harry Hines Boulevard, Dallas 19.

University of Wisconsin Medical School, Madison: Postgraduate courses for 1958-1959:

Advances in anesthesia and resuscitation, October 10-11
General practice—1958, November 6-8
Hematology and hypertension, March 19-21
Problems of the newborn period, April 2-4
The pathology and radiology of the skeletal system, May 21-23

For further information, write to: Dr. Robert C. Parkin, Coordinator, Postgraduate Medical Education, 418 North Randall Avenue, Madison 6.

Woman's Hospital, New York: Postgraduate courses limited to general practitioners, October 16-30:

Antepartum care
The conduct of labor and delivery

For further information, write to: Mr. Carl P. Wright, Jr., Woman's Hospital, 141 West 109th Street, New York 25.

Curariform Drugs and the New Hypothesis Concerning Neuromyal Transmission

A. ROSS McINTYRE*

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In 1942 Griffith and Johnson published their important paper entitled "The use of curare in general anesthesia," and that year marked the beginning of large-scale clinical use of curare. It followed closely the revival of interest in this drug resulting from West's work with King's *Chondrodendron* alkaloids and the independent studies by Bennett and associates, who in 1940 first used curare for the control of convulsions in shock therapy.[1] Last year, 15 years after Griffith and Johnson's paper and 21 years after West first used d-tubocurarine in man, the International Symposium on Curare and Curare-like Agents was held in Rio de Janeiro. Almost every country was represented, and a curare bibliography compiled for the meeting contained nearly 3000 references. I will attempt to summarize some of the clinical and pharmacologic material presented at this meeting and at others during the past few years.

Intocostrin® and d-Tubocurarine

Almost all of the curare used in clinical work beginning in 1942 was a partially purified aqueous extract known as Intocostrin. Intocostrin was the commercial name given to the early aqueous curare extracts used by Bennett and associates and first prepared in the Department of Physiology and Pharmacology at the University of Nebraska College of Medicine. It was standardized by the rabbit "head-drop" method devised by H. A. Holaday of the Squibb Research Laboratory; details will be found elsewhere. Intocostrin was the only standardized preparation commercially available at that time. Later the efforts of Win-

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tersteiner and Dutcher, following the pioneer work of King, resulted in the preparation of d-tubocurarine in commercial quantities, and this alkaloid gradually supplanted the partially purified extracts previously used.

With the availability of the active alkaloid d-tubocurarine for research purposes, it soon became evident that the hypotensive effects often observed in association with use of the earlier curare mixtures and generally attributed to the presence of tertiary amines (curines) were in fact partly the result of the release of histamine that sometimes is observed following d-tubocurarine injection. These effects are especially likely to occur if the rate of administration is too rapid or if the dose is too high.

Synthetic Substitutes for Natural Curare Alkaloids

Although the principal alkaloid from *Chondrodendron tomentosum* was first isolated in England by King, initially, for various reasons, supplies of d-tubocurarine were less readily available in Europe than in the United States. It is not surprising that efforts to synthesize substitutes for the natural alkaloid were pursued energetically, particularly in Great Britain and France. As a result, 1948 and 1949 saw the introduction of the methonium compounds by Barlow and Ing and by Paton and Zaimis. It was soon realized that the curariform potency of these compounds, which are polymethylene bis-trimethyl ammonium salts, depends in part on the length of the carbon chain joining the two quaternary nitrogens. The most potent compound has a straight chain of 10 carbons and is often referred to as decamethonium. Workers found that these same compounds have a powerful autonomic ganglion-blocking action when the carbon chain is shortened. The optimal carbon chain length for these compounds is six carbons (hexamethonium).

In a few years, Bovet* synthesized gallamine, more widely known as FLAXEDIL®. This compound is considerably more complicated in structure than decamethonium and has a somewhat more general cholinergic blocking activity than d-tubocurarine. The resulting loss of vagal tone may produce marked tachycardia.

In contrast to Flaxedil, Myotolon, introduced in the United States in 1950, at first stimulates autonomic cholinergic receptors. Consequently both bradycardia and increased salivation are frequently observed, necessitating the use of atropine. In unanesthetized patients this compound may produce marked nausea and vasomotor disturbances.

In 1949 it was found that succinylcholine, also known as diacetylcholine, has curariform properties; this substance had been recognized chemically since Hunt's work in 1906. It was introduced into clinical use almost simultaneously in many countries on both sides of the Atlantic. It is perhaps the most successful of the synthetic curariform compounds but it is not innocent of unwanted side effects. Indeed it has a powerful if somewhat fleeting depressive effect on the central nervous system, which may result in sudden cessation of respiratory movements caused by a disturbance of respiratory reflex mechanisms. This occurs before noticeable *peripheral* effects develop, and artificial support of respiration is, of course, often necessary.

The steadily increasing use of curariform drugs during the 15 years since Griffith and Johnson's contribution has quite naturally aroused discussion. The essential question is this: Can these compounds increase muscle relaxation without at the same time unduly increasing the risk to the patient? There is a consensus that the answer is affirmative, and the tendency is to use lighter degrees of anesthesia than were possible formerly and at the same time to lower muscle tone with the curariform agents. Discovery of the short-acting diacetylcholine compounds has increased the feasibility of controlling muscle tone precisely and accurately for the requisite periods.

Use of curariform drugs in anesthesia has not been without its critics, and some of these are highly respected specialists. For example, Beecher stated that he believed the use of curare in anesthesia increases the risk,[2] and it is certainly true that use of these compounds

*While this article was being prepared, Professor Bovet received the Nobel prize for his work in this field.

in a rash and improper manner can be dangerous. One should never use them unless adequate experience and equipment are available to sustain respiration artificially. With experience and the necessary equipment, most anesthesiologists agree that use of curariform drugs is an extremely important and valuable addition to anesthesia. The long-known superiority in muscle-relaxing property of ether anesthesia is now recognized as a curarelike action which lowers the tolerance for the curare drugs.

Uses of Curare and Synthetic Substitutes

Whereas the most extensive clinical field for the curariform drugs is anesthesia, several other uses continue to have clinical value and great scientific interest. For example, their use in shock therapy, which ushered in the modern application of muscle-relaxing agents, has been enhanced by the development of short-acting compounds such as succinylcholine. This substance is destroyed, presumably by hydrolysis at its ester linkage by esterases, and therefore recovery from its effects usually is very prompt. This property makes it ideal for use in shock therapy to protect the patient against fractures and other damage to bones and ligaments during the brief period of convulsions. Similarly, curare drugs are invaluable in reduction of dislocations, relief of muscle spasm, and setting of fractures. Employment of the longer-acting compounds for muscular tension and pain is well established in orthopedic practice. They often afford striking relief, and the period of relative freedom from pain often far outlasts the apparent duration of muscular relaxation.

Borromea first reported the use of curare in intractable hiccups,[3] and her findings have been abundantly confirmed. The temporary loss of diaphragmatic tone usually terminates the attack.

In the diagnosis of myasthenia gravis, d-tubocurarine continues to be widely employed; great caution is necessary in injecting the drug for this purpose. I have found that d-tubocurarine also can be of value in differential diagnosis of other neuromyopathies. For example, when a concentric needle is inserted into a muscle, the injection of d-tubocurarine can aid in distinguishing between fasciculation and true fibrillation. If fasciculation is present, the d-tubocurarine promptly abolishes its electromyographic pattern; the drug has no effect on true fibrillation unless excessively large—in fact, dangerous—doses are used. Thus d-tubocurarine does not easily interrupt true fibrillation which results from either temporary or permanent denervation, but it promptly inhibits other spontaneous activity such as fasciculation. Indeed, it is as a physiologic and pharmacologic tool that these compounds have proved invaluable to all those interested in elucidating the mechanisms of neuromuscular excitation and contraction; but it is important to remember that the various curariform compounds have different mechanisms of action and yield a variety of results when used as diagnostic tools.

Mode of Action

Current concepts of the mode of action of curare compounds leave much to be desired and it is unwise to assume that we can divide them simply into acetylcholine-blocking agents and depolarizing agents. Although it is true that d-tubocurarine may exert most of its action by blocking access of the chemical transmitter to the muscle sole-plate and that decamethonium interrupts the transmission by depolarizing the end-plate area, many quantitative differences exist among the various compounds and the response of different species varies considerably. For example, in birds decamethonium produces muscle spasm and opisthotonos. Further, it has been shown that the period of interruption of neuromuscular transmission produced by decamethonium outlasts the time during which depolarization of the junctional tissue occurs. Hence the mechanism by which the "depolarizing" compounds induce prolonged neuromuscular paralysis is not yet fully elucidated and must await a more complete understanding of normal neuromuscular transmission. These differences have many practical applications. For example, it is well known that PROSTIGMIN® is not an antidote for the so-called depolarizing agents such

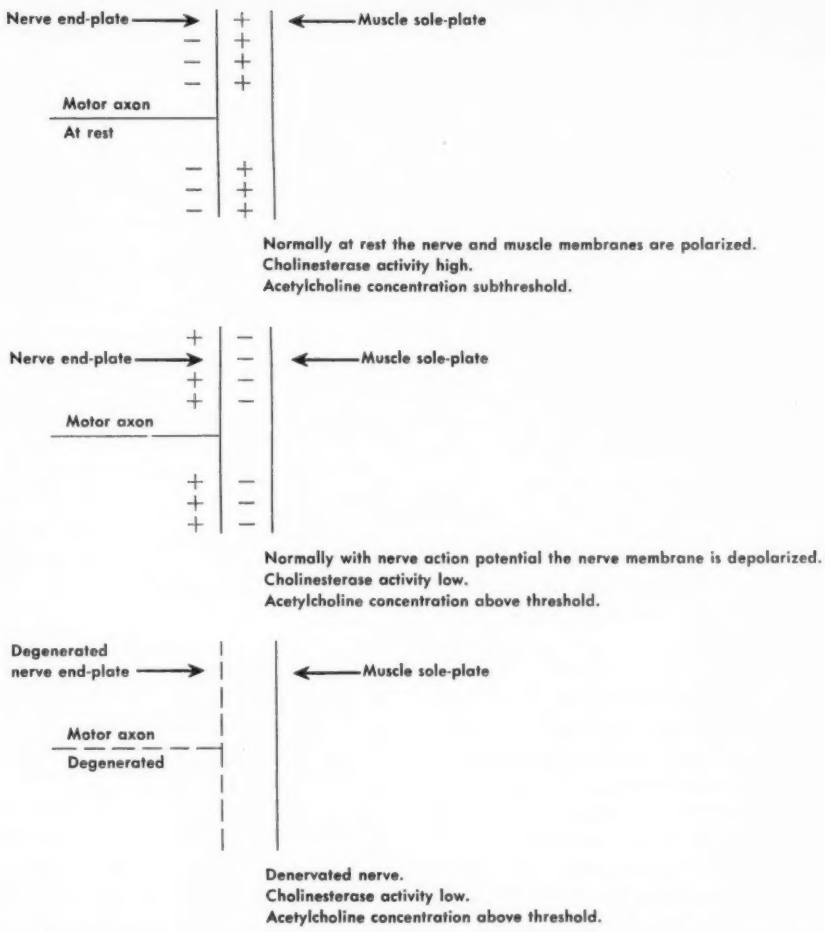
as decamethonium and succinylcholine. Sometimes, however, succinylcholine, normally a compound with short duration of effect, may have an unduly prolonged action, for some unexplained reason, and I know of a few cases in which respiration was impaired for several hours and in which the administration of Prostigmin brought about improvement. It seems that such patients may have some unrecognized neuromyopathy.

The Classical Chemical-transmitter Theory

The classical theory of chemical transmission at the neuromyal junction, briefly stated, holds that the transmitter acetylcholine "released" as a consequence of a motor nerve impulse reaching the motor nerve end-plate depolarizes the muscle sole-plate and arouses the onset of a muscle action-potential associated with contraction of the muscle cell. This theory explains many of the observed phenomena at the junctional tissue including curarization by d-tubocurarine and other transmitter-blocking agents. It is believed that the curare alkaloid is bound by the "receptor substance" in the sole-plate normally acted on by the acetylcholine, whose action is thus blocked.[4] The mechanism of action of the depolarizing compounds also may be made to fit the theory reasonably well. The initial transient increase in response after small doses of decamethonium can be explained on the basis of the depolarizing action of the drug causing additive effects with the transmitter acetylcholine. Later the junctional region becomes further depolarized, and because decamethonium is a relatively stable compound there is no ready means by which the tissues can eliminate it rapidly. Time must elapse for it to be eliminated gradually and for the muscle sole-plate again to become responsive to the transmitter. The fact that this type of drug sometimes continues to prevent indirect excitation after the junctional region has become *repolarized*[5] is more difficult to explain; it becomes necessary to attribute to decamethonium an acetylcholine-blocking mechanism or possibly some other unknown action to explain the long-persistent block. However, it appears that this latter action differs from that which is produced by d-tubocurarine, as Prostigmin is not considered a reliable antidote.

Denervated muscle—In contrast to normal muscle, the known phenomena concerning the reaction of denervated muscle to acetylcholine, the curariform drugs and anticholinesterase compounds are difficult to reconcile with the chemical mediator theory in its present form. For example, one would expect that denervated muscle would require *increased* amounts of acetylcholine to cause it to contract. The opposite is true; the denervated muscle is about a thousandfold more sensitive to transmitter, and, further, the effect of intra-arterially injected acetylcholine is prolonged many times over that seen in normal muscles. It has been shown that curare and acetylcholine are mutually antagonistic, and the relative ineffectiveness of curare to elicit a response in denervated muscle is indicative of the presence of more, not less, transmitter than in innervated muscle.[6] Again, the effects of anticholinesterase drugs on denervated structures are markedly less than normal,[7] as would be the case if cholinesterase activity were absent or markedly reduced.

This apparent failure of the classical theory to fit the known facts concerning the behavior of denervated muscle has resulted in a reexamination of the question of the presence of transmitter (acetylcholine) in normal and denervated dogs' muscles. The detection of acetylcholine in perfusates from muscles is always difficult.[8] Most investigators who have attempted to demonstrate acetylcholine in muscle venous blood have been prevented from doing so by the presence of considerable quantities of specific cholinesterase in red blood cells and the presence of nonspecific esterases in the plasma and junctional tissue of the muscle. To demonstrate acetylcholine in muscles, they must be perfused with eserinized "physiologic" solutions; this results in rapidly increasing degrees of muscle hypoxia. Under these circumstances it is not surprising that the demonstration of acetylcholine in muscle perfusates is difficult, and success depends to a degree on the length of time the muscles have been subjected to perfusion.



The nerve end-plate and the muscle sole-plate are contiguous membranes. They are in close proximity and they form the nerve-muscle junction.

FIGURE 1

Detection of Transmitter in Muscle Perfusates

Fortunately there are now available extremely sensitive biometric technics for the detection and quantitative determination of acetylcholine. One of the most sensitive bioassay methods is provided by the exposed and excised heart of the quahog, or clam, *Venus mercenaria*.[9] This tissue will readily exhibit inhibition by concentration of acetylcholine as low as one part in 10^{-10}. By taking advantage of this extremely sensitive method it has been possible to re-examine the question of transmitter in perfusates of dog muscle, and it has been demonstrated that acetylcholine is present in both normal and denervated muscles.[10] This finding, at first glance, appears to throw doubt on the chemical-transmitter theory, a theory that has stood the test of more than 20 years and is now almost universally accepted. However, the behavior of denervated muscle can be harmonized with the classical chemical-transmitter theory.

A New Hypothesis Concerning Chemical Neuromyal Transmission

The aforementioned difficulty can be resolved by a new and simple hypothesis concerning the initial step in the classical theory. If, instead of postulating that as a result of depolarization of the nerve end-plate acetylcholine is rapidly *produced*, an alternate assumption is made that the *activity* of cholinesterase is suddenly *suppressed*, thus allowing a rapid increase in concentration of acetylcholine, the sequence of events as described in the classical theory will then automatically follow. Measurements of total cholinesterase content of denervated muscles have yielded inconsistent results. However, the difficult task of directly measuring cholinesterase *activity* in vivo apparently has not been attempted. Nevertheless it seems incontrovertible that whatever the total cholinesterase content of denervated muscle may be, when measured on denervated muscle brei, the fact remains that cholinesterase is relatively inactive *in situ*; otherwise the great sensitivity of denervated muscles to acetylcholine would not be seen.

This hypothesis overcomes the difficulties of explaining the spontaneous activity and greatly increased sensitivity of denervated muscle to acetylcholine. In addition, many of the well-known actions of the curariform and related drugs on denervated muscle are more easily comprehended. Thus the relative ineffectiveness of anticholinesterase drugs in denervated structures would naturally result from the markedly lowered activity of cholinesterases; and the relative ineffectiveness of curare to prevent fibrillation in denervated muscle is attributed, in part, to the higher than normal concentration of acetylcholine consequently present at the muscle sole-plates. Finally, the temporarily augmented muscle-response to indirect stimulation, seen shortly after cutting the motor nerves, is explained by the gradual impairment of the normal motor end-plate structure whose integrity is necessary, according to this new hypothesis, for normal cholinesterase activity at the junctional tissue. This hypothesis is made not in the belief that it will provide a complete answer to all the complexities of neuromyal transmission but rather in the hope that its presentation may stimulate further work that may help solve the many unexplained questions on this subject.

Summary and Conclusions

The growth in the clinical use of curare and related compounds is described and evaluated, and the importance of these compounds as pharmacologic and diagnostic tools is emphasized. The chemical transmission theory of neuromyal conduction is discussed and a new hypothesis concerning the normal role of the motor end-plates is presented. This new hypothesis serves to explain the hypersensitivity of denervated muscles to acetylcholine and the hitherto unexplained actions of the curare drugs on denervated muscles. It is believed that the hypothesis strengthens the basic concept of chemical mediation of transmission at the nerve-muscle junction.

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Drug Reactions

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A DISTURBING and often serious therapeutic complication is the development of an unanticipated reaction to the medication. While the term "reaction" includes manifestations in every tissue and organ of the body, I will limit this discussion primarily to cutaneous lesions. It should not be inferred that because only a cutaneous manifestation is mentioned there may not be concomitant disturbances in other tissues.

ADOLPH ROSTENBERG, JR.

Mechanism of Drug Reactions

In the present state of knowledge it is not possible to state with certainty the pathogenesis of all drug reactions, but we may offer reasonable hypotheses to explain certain of them.[1-4] Some of the more important mechanisms are (1) enzymatic interference, (2) allergic sensitization, (3) a Shwartzman reaction, (4) a Herxheimer reaction and (5) ecologic interference. It is important to realize that such diverse mechanisms can bring about drug reactions and that it is an erroneous oversimplification to assert that a patient is allergic to a drug merely because some sort of reaction develops while he is taking it. A decision as to the mechanism of a given reaction is not merely a bit of useless theoretical information but may be of direct importance to the patient inasmuch as it may determine whether the drug in question can be continued. Admittedly such a decision often is difficult or impossible but this does not mean that one should not strive to make it.

Enzymatic interference or competition—A large number of drugs achieve their therapeutic objective or pharmacologic effect by interference with some enzyme system either in the host or in the invading organism. It is increasingly apparent that various side reactions are the unexpected consequence of a host enzymatic interference. For example, such an effect can bring about pseudovitamin-deficiency states. If a given vitamin is necessary for the proper functioning of an enzyme system and a given medication interferes,

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FIGURE 1. Generalized, symmetrically distributed papulopustular eruption which developed after taking some proprietary tonic.

then, even though intake of the vitamin is adequate, lesions will develop that are analogous to those seen when intake of the vitamin is inadequate. It has been suggested that some of the cutaneous lesions developing after use of heavy metals, lesions which resemble those seen in ariboflavinosis, arise by such a means. Recently, Motulsky[5] in an interesting article suggested that a possible explanation for some drug reactions may be that the persons in whom they develop are biochemical deviants. Under ordinary conditions this deviation does not produce overt manifestations, but under conditions of stress (in this case, exposure to a particular drug) the result is different.

Notice that the words "idiosyncrasy" and "intolerance" are not listed among the mechanisms for the production of a drug reaction. These labels, while having the sanction of tradition, were merely cloaks for ignorance. With increasing knowledge many manifestations that were at one time labeled intolerance or idiosyncrasy can be more properly placed under other headings. Motulsky suggested that some of the reactions that have been labeled as idiosyncratic may be examples of biochemical deviation.

Allergic sensitization—I have already stated that it is an error to assert that a patient is allergic to a drug merely because some sort of reaction develops after he takes it, but this does not mean that some drug reactions are not brought about because of allergic sensitization. Actually, some of the most serious reactions arise by this means. To state that a reaction is allergic implies that an antibody system mediates the reaction; however, this does not signify that a circulating antibody will necessarily be demonstrable.[6,7]

Shwartzman reaction—A Shwartzman reaction is a hemorrhagic necrotic reaction brought about by a bacterial product (preparatory factor) rendering the treated tissue more vulnerable to proteolytic enzymes. The subsequent intravenous administration of another Shwartzman filtrate (eliciting factor), by lowering the titer of proteolytic enzyme inhibitors and causing the formation of leukocytic platelet clumps which become sequestered in the prepared tissue, produces extensive damage there. It has been shown that the union of an antigen with its antibody produces the same effects as the Shwartzman eliciting factor, so that if a prepared site exists damage may occur. It should be evident that such a mechanism is a serious potential menace in any infection for which the patient receives a drug to which he may be sensitive. Purpura and cutaneous ulcerations may result. Some of the widespread systemic vascular reactions which are seen with increasing frequency may also be on the basis of a Shwartzman reaction.[8]

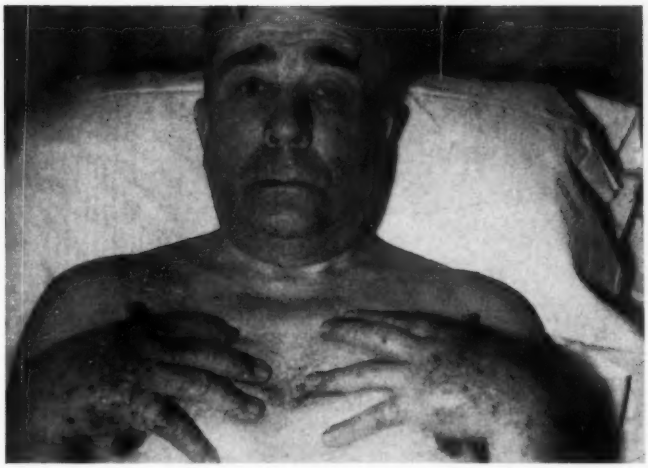

FIGURE 2. Widespread, symmetrically distributed eruption in which the lesions are not as numerous as they are in the eruption illustrated in figure 1. This eruption developed after one of the sulfonamides.

Herxheimer reaction—A Herxheimer reaction denotes one caused by the wholesale slaughter of microorganisms with the consequent release of toxic or allergenic material which in turn can produce reactions by any of the aforementioned mechanisms.

Ecologic interference—It is becoming increasingly appreciated that ecologic interference may play an important role in the pathogenesis of disease. The delicate balance that exists between the host and certain microorganisms which under usual conditions are only quasipathogenic can, by virtue of drug therapy, be easily upset, with the conversion of the quasipathogen into a full-blown one.[9] Torack[9] suggested that we should distinguish between surface proliferation of fungi and invasiveness into tissues. He expressed the belief that the former occurs when antibiotic therapy alone is employed and that the latter is associated with combined antibiotic and steroid therapy. Torack's article covers this complication only with respect to fungi, but the same general principles apply to many bacterial species, for example, *Pseudomonas* and *Proteus*.

Morphology of Drug Reactions

A drug eruption is formally labeled as a dermatitis medicamentosa, a term which denotes a more or less generalized symmetrical, slightly bizarre eruption; but drug eruptions can mimic the appearance of any dermatosis, and while they often produce widespread and symmetrically distributed eruptions they by no means invariably do so. Hence one will miss the diagnosis of a drug reaction if one makes it only when such a distribution is seen.[10-14] The more common morphologic varieties of drug eruptions are (1) erythematous or exanthematous, or both, (2) eczematous, (3) urticarial, (4) erythema multiformelike, (5) acneiform, (6) lichenoid and (7) fixed. Certain drugs tend to produce a particular morphologic response but this is only generally true, and probably any drug can occasionally cause any type of cutaneous lesion.

An erythematous or exanthematous drug eruption is one in which the basic component is an erythema, on which other lesions such as papules or vesicles may be superimposed. The lesions are usually widespread. Figure 1 illustrates such an eruption. Scaling is part of the reaction, and if it is severe enough the process is labeled an exfoliative dermatitis.

An eczematous drug eruption is one in which there are areas of closely aggregated papules and vesicles. On section, spongiosis would be seen. This type of reaction is quite akin to the previous one, the chief difference being that the patches of eczema tend to be discrete and as a rule the total amount of cuta-

FIGURE 3. Fixed drug eruption from phenolphthalein. The pigmented lesion over the dorsum of the hand and the one in the neck flared each time the patient ingested the medication.

neous involvement is less. The lesions are, on the whole, moister. The classic example of this variety is a contact dermatitis from the external application of a medication, but the same type of lesion can develop from the internal administration of a drug. Arsphenamine, the sulfonamides and the modern antituberculosis drugs are outstanding examples of drugs that can produce this type of reaction. Figure 2 is an example of this type of lesion.

An urticarial reaction is one that consists of wheals. The intervening skin may be normal or slightly erythematous. The distribution of urticarial lesions is not pathognomonic except that lesions are more likely to develop at points of pressure. If the location of the wheal is rather deep there will be a diffuse edematous appearance known as angio-edema. If the urticarial reaction is very acute, especially in a child, there may be a bullous element. There nearly always is intense pruritus.

The basic lesion of erythema multiforme is a succulent erythematous papule, often with a slight hemorrhagic element. Such papules will start to involute but a recrudescence in and around them gives the appearance labeled an "iris lesion," meaning that not infrequently there is a marked resemblance to the iris. In addition to the cutaneous lesions there often are mucosal lesions.

The essential lesion of acne vulgaris is the comedo, superimposed on which there may be secondary infection with the formation of a typical acne pimple. In acneiform drug eruptions the comedo is, as a rule, not seen. What actually develops is a pustule resembling that seen in acne and often located in the areas usually affected by acne.

A lichenoid eruption is one in which tiny papules form which tend to become aggregated. The eruption is a dry one. Such papules constitute the principal features of the eruption and do not metamorphose into some other morphologic form.

The term "fixed drug eruption" denotes an erythematous macule which becomes pigmented. The term "fixed" indicates that each time there is an exacerbation the old sites flare. Initially there may be only one or two macules, and these may disappear if the intervals between contact with the offending agent are long enough. If exposures are repeated frequently enough the lesions may stay pigmented and new ones may appear, so that ultimately large areas of the body may be covered. Figure 3 illustrates the morphologic features.

Drugs Causing Reactions

While any drug can cause reactions, it is a commonplace that certain ones are much more likely to do so. Just why certain drugs have this propensity is not known. In allergic-type reactions one could argue on theoretical grounds that certain drugs are more likely to form appropriate antigenic combinations with body proteins and hence sensitize the host. Also on theoretical grounds, one might argue that certain drugs are more likely to affect various enzyme systems and bring about reactions by such a mechanism. While both these concepts have theoretical validity, the present state of knowledge does not permit a prediction on the basis of the chemical configuration as to whether a given drug is more likely to produce reactions and, if so, what kind.

I shall now discuss briefly the cutaneous reactions produced by a few drugs or groups of drugs.

Antibiotics—From the point of view of reaction-producing propensities we can divide the antibiotics into two groups: (1) penicillin and streptomycin and (2) the rest. There is no question that penicillin is very prone to sensitize. One need only look at the medical literature to see the increasing number of reports of reactions to it. Corr and Wellman,[15] in reviewing the literature on penicillin reactions, presented tables that illustrate the alarming increase in their occurrence.

The wide use of penicillin and the increasing use of forms that are slowly excreted so that contact of the drug with body tissues is vastly prolonged greatly enhance the likelihood of development of sensitization. Streptomycin probably is just about as good a sensitizer as is penicillin but by virtue of its much more limited use the number of reactions encountered is considerably less.

The remaining antibiotics are by and large much less likely to cause reactions, particularly of an allergic nature. The most important side reaction seen with their use is the development of complicating infections, e.g., monilial, presumably from ecologic interference. The foregoing remarks apply to the systemic administration of these drugs. Topical application of most of the antibiotics is to be frowned on, because it increases the likelihood of an allergic sensitization of the delayed type, which might interfere with subsequent systemic use of the drugs. Further, one can obtain any therapeutic effect just as well with other agents. Some of the antibiotics which have been considered quite safe for topical administration, e.g., neomycin, have recently become suspect with respect to their cutaneous reaction-producing propensities.

Tranquilizers—The tranquilizers, namely, chlorpromazine, meprobamate and reserpine, are a group of drugs possibly second only to the antibiotics in terms of current use. These drugs are fairly likely to produce reactions but these as a rule are noncutaneous.[16,17] The most important and frequent cutaneous reaction is photosensitivity, with development of maculopapular, somewhat urticarial eruptions, chiefly over the face, upper extremities and trunk. In most cases in which photosensitivity has developed the drug has been discontinued, but some patients have continued to take the drug without apparent adverse consequences.

Antituberculosis drugs—The antituberculosis drugs, namely, streptomycin, isoniazid and its relatives, and para-aminosalicylic acid, are usually given in combination in treatment of pulmonary tuberculosis. Cutaneous reactions from them are seen quite frequently. The lesions are of various kinds but the most common ones resemble an infectious eczematoid dermatitis. As a rule, such a reaction is not severe enough to warrant discontinuing the antituberculosis medication, but occasionally this is necessary. These medicaments, of course, may produce other manifestations such as a hepatitis.

Antipyrine and phenolphthalein—These drugs, while much less important therapeutically than those so far considered, will be discussed because of the interesting and peculiar types of reactions they occasionally elicit. A fixed drug eruption may develop with either of them. Many agents besides the two mentioned can also cause fixed drug eruptions, e.g., arsphenamine, sulfonamides and antibiotics. It is well to remember the possibility of a fixed drug eruption from a proprietary laxative when a woman complains of pigmentation around the eyes, especially if she has a spot or two of pigmentation elsewhere.

Either antipyrine or phenolphthalein can bring about an erythema multiformelike syndrome, but this reaction is more commonly seen after antipyrine. The antipyrine often is encountered in proprietary mixtures, such as 666® for colds.[18] The reaction can be quite serious and fatalities have been reported. Sometimes there are typical erythema multiformelike lesions on the skin but the eruption may consist merely of oral and genital lesions.

Bromine and iodine—Reactions to bromine and iodine are not infrequently encountered. These drugs can produce a variety of reactions, the most frequent of which are (1) an acneiform eruption, (2) nodose ulcerative lesions and (3) a toxic bullous eruption. The nodose ulcerative lesions deserve special emphasis because they are frequently misdiagnosed. Morphologically there are usually only

FIGURE 4. Nodular ulcerative bromoderma. This is the type of lesion that may be confused with a simple pyoderma, blastomycosis or a squamous cell carcinoma.

a few lesions and they tend to appear on the extremities, especially the lower. The lesions may be fungating or crusted ulcerations. Such a lesion is shown in figure 4. The conditions with which they are often confused are (1) ordinary pyoderma, (2) blastomycosis and (3) squamous cell carcinoma.[19] An ordinary pyoderma will not present the fungating appearance that the lesion of bromoderma may show. If the pyoderma is of any size there will be inflammation in the surrounding skin as a cellulitis. In blastomycosis there are small pustules at the periphery of the lesion, which tends to have a sloping palisade. The fungal elements are ordinarily demonstrable in smears from such lesions. The most serious confusion is with a squamous cell carcinoma. The confusion arises because the proper diagnosis is not considered and the lesion is treated, say, as a simple pyoderma, and because of its intractability and its fungating appearance the physician becomes more and more suspicious of a neoplasm. A biopsy is performed, but unfortunately the section shows a pseudo-epitheliomatous hyperplasia which, as the name implies, can be mistaken for a true epithelioma. The diagnosis of an epithelioma is apparently confirmed, leading to disastrous therapeutic recommendations.

In the diagnosis of a bromoderma it is often advocated that a serum bromide level be obtained.[18] This is dubious advice, because while an elevation in the serum bromide level often exists in the presence of a bromoderma there is no particular level that is required. More important, a person taking bromides will have an elevated serum bromide level but obviously any other kind of skin lesion can develop at such a time. Suppose a true squamous cell carcinoma develops on an extremity of a person who is taking bromides; a slavish adherence to the serum bromide level for diagnosis would be catastrophic.

Diagnosis of a Drug Eruption

Diagnosis of a drug eruption depends primarily on the alertness and suspicion of the attending physician. There are no pathognomonic signs by which one can diagnose a drug eruption with certainty. In any widespread, symmetrically distributed, somewhat bizarre eruption, one should think of dermatitis medicamentosa, but it is not necessary for the eruption to be widespread or symmetrically distributed; further, remember that eruptions caused by drugs can mimic any other eruption.

One must obtain a painstaking history. It does not suffice to ask the patient, "Do you take drugs?" or to let it go with a categorical denial. The physician should inquire, "When you have a headache, what do you take? Do you ever take aspirin, ALKA-SELTZER®, BROMO-SELTZER®, etc.?" "What do you take when you have heartburn or acid in your system?" In each case the physician should enumerate several proprietary products to refresh the patient's memory. System by system should be methodically gone over. Remember that drugs do not have to be ingested. A scalp lotion or a vaginal douche or a salve for athlete's foot may be the source of the trouble. Occasionally a patient may be unaware that he has come in contact with a drug; for example, after a tooth extraction a sulfonamide could have been put in the socket. If the eruption appears to be on a drug basis but the history fails to elicit any possibilities, the questioning must be repeated until it is evident that further interrogation would be futile.

If the patient has taken a drug, that in no way proves that the drug caused the eruption. Obviously a history of taking bromides and the presence of one or two nodular ulcerative lesions of the type that are known to develop from bromides provide a reasonable presumption that the skin lesions and the drug are associated. On the other hand, a widespread maculopapular eruption in a patient who takes a barbiturate occasionally does not constitute proof that the barbiturate is responsible for the eruption. How, then, does one prove that a given drug actually is responsible for an eruption? In advance let me state that I do not believe this can be done with absolute certainty. By and large, skin tests are not of particular value in demonstrating the etiologic role of a given drug. The only evidence that establishes a causal connection is the cessation of the eruption when the drug is discontinued and its recrudescence when the drug again is administered. Let me hasten to add that I believe that only half of this investigation should routinely be done. In other words the chain of proof in clinical medicine should end with the improvement of the eruption when the drug in question is discontinued. It is far too hazardous a procedure under ordinary circumstances to complete the chain by readministering the drug.

Therapy of Drug Eruptions

The therapy of drug eruptions can be considered under five headings which as a mnemonic device can be labeled the "A, E, I, O, U" of drug-reaction therapy.[20] "A" stands for avoidance, which merely means that the suspected drug is to be avoided. Today, with the wide choice of medications for the majority of conditions, substitution as a rule presents no problem.

"E" stands for elimination or eradication, which denotes using other drugs that will either expedite removal of the offending drug or destroy it. An outstanding example of a drug that expedites the removal of another drug is British anti-lewisite; in the treatment of acute reactions from heavy metals it may be lifesaving. Unfortunately, for most drugs there are no agents of particular value in speeding their removal. Recently, penicillinase has been suggested for the treatment of penicillin reactions; this enzyme is known to destroy penicillin.[21]

"I" denotes immunologic therapy, in this case desensitization. This is a controversial point. First of all, desensitization is applicable only to a drug reaction brought about by an allergic sensitization. Such a therapeutic approach has no rationale in a drug reaction caused by other mechanisms, which is one of the important reasons why the diversity of mechanisms in pathogenesis of drug reactions was emphasized. In theory, desensitization would seem to be a reasonable procedure in an allergic drug reaction. In practice, this is questionable. I should like to emphasize that desensitization is a hazardous procedure and that even if successful it will probably have to be continued more or less indefinitely to preserve the so-called desensitized state. The two drugs concerning which desensitization procedures have been reported most frequently are penicillin and streptomycin.[22-25]

To sum up, desensitization is recommended only as a last resort if substitution is not feasible, for one or another reason.

"O" stands for obstructive therapy, or the use of measures that tend to block or antagonize the mechanisms by which the drug produces its reaction or to ameliorate or assuage the inflammatory consequence of such a reaction. Under this heading are included most of the systemic measures used in treatment of drug reactions. For example, epinephrine is a physiologic antagonist to histamine, but epinephrine is not advocated for ordinary urticaria or serum sickness. Its effects are too evanescent and potentially too dangerous. The antihistaminic drugs achieve their effect, as is well known, by competing with histamine for a site of action. They are primarily of value in treatment of urticarial reactions. As topical agents they have little or no value. The corticosteroids are indicated in severe types of drug reactions and may be lifesaving, but it is not advisable to use them for any trivial eruption.

Finally, "U" stands for unguental or the usual topical therapy, including any topically

applied medication. The primary symptoms in drug reactions are itching and burning. Unfortunately there are no agents that are very efficient against itching. Colloid baths have some soothing and antipruritic qualities. A colloid bath is prepared by adding approximately a double handful of prepared starch or oatmeal to a three-quarter tubful of lukewarm water. Various "caine" derivatives can be used. While many of these have a reasonably good temporary antipruritic effect, they are all potentially hazardous in that they are apt to sensitize. One should also remember that the inflamed skin apparently is more vulnerable to development of sensitization. Systemic sedatives or tranquilizers often are useful adjuncts.

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MEETINGS and Postgraduate Courses

The New York Academy of Medicine, New York: Second annual postgraduate week, October 13-17. The course presented will be on research contributions to clinical practice. For further information, write to: Secretary, Postgraduate Week, The New York Academy of Medicine, 2 East 103rd Street, New York 29.

University of Nebraska College of Medicine, Omaha: Postgraduate courses for 1958-1959:

Hematology, October 15-16
Psychiatry and neurology, December 4
Obstetrics and gynecology, January 15-16
Physical medicine and rehabilitation, February 26
Obstetrics, March 26
Pediatrics, April 13-14
Seventh Annual Spring Postgraduate Assembly and Poynter Lectures, April 15-17
Anesthesiology, May 5
Fourth annual trauma day, May 6

For further information, write to: Office of Postgraduate Affairs, University of Nebraska College of Medicine, 42nd and Dewey, Omaha 5.

The Practice of Toxicology

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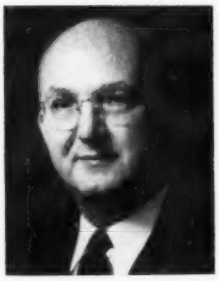

WALTER J. R. CAMP

CLINICAL toxicology is that branch of medicine concerned with prevention, diagnosis and treatment of conditions produced by poisons. It may be considered a recently emerging discipline, although the poisonous actions of many plants and chemical substances have been known since the earliest time of written history.

One may define a poison as any chemical substance which, under given circumstances, effects morbidity or death when it is ingested or when the body is exposed to it. At least two reasons may be given for the current interest in toxic materials. One is the introduction by industry, with astonishing rapidity and profusion, of products containing toxic substances and made readily and attractively available to the public. Another is that with the reasonable control of contagious diseases and the advent of antibiotics which control many infections, concern is increasing for the problems of accidents and toxic products.

This concern is reflected by the establishment of the Poison Control Center originated by Dr. E. Press under the aegis of the American Academy of Pediatrics, now numbering over 100 units, and by the appointment of a Committee on Toxicology by the American Medical Association. Legal medicine, however, too often is ignored in the medical curriculum, although it is an area of major concern to the practitioner.

Since most cases of accidental poisoning involve children, it is not surprising that pediatricians have led the way in recognizing a responsibility for the correction of this problem. It cannot be overemphasized that the large majority of cases of poisoning in children are without doubt preventable. And one may add that poisoning in adults, other than instances of indisputable suicide, is equally preventable.

With poisoning on the increase, it is imperative that the medical profession in general become more alert to the ravages of toxic substances. It is just as important to know the symptoms induced by extraneous chemi-

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cal substances as it is to recognize those of infectious and other diseases. We can no longer assume that poisoning is uncommon. Such an attitude can permit the problem to expand disastrously to major proportions. The medical profession must now consider poisoning just as important as any other area of medicine.

There is a degree of overlapping in the three functions of toxicology: that of medical practice, that of industry, and that of the analytic chemist. The average practitioner must be aware that a patient's symptoms may be due to intoxication of industrial origin even when he is no longer associated with industry. Inquiry into a patient's industrial history often reveals the source of indefinite or bizarre symptoms. However, one should not jump to unwarranted conclusions on the basis of such a search. The fact that a patient was or is a painter does not permit the conclusion of lead intoxication, since many paints do not contain significant amounts of the metal and in many instances the solvents used are of greater toxicologic significance than the lead. Nor should one dismiss a consideration of poisoning if the patient is a housewife, because the home probably contains more poisonous substances than any other social area. It is vastly more important to know just what a person does at a given occupation than to know what the occupation is. Surprisingly, many workers handling toxic materials in industry have not the least idea what the materials are or of the dangers associated with them. While reputable manufacturers have safety engineers, physicians and others to establish proper care of the employees, many small concerns do not have such safety control and some, through either ignorance or indifference, make no attempt to protect those exposed to noxious substances. Thus a meticulous inquiry into the work habits is of prime importance in the diagnosis and care of a patient whose symptoms or signs may be due to poisoning.

Prevention of Poisoning Through Education of Patients

Prevention of poisoning, like prevention of disease, is infinitely more rewarding and gratifying than treatment of a condition after it occurs. Programs of mass education have their limitations and sometimes one wonders if any impression is made. Progress has been made in such fields as poliomyelitis and tuberculosis, but one continues to read daily of persons convicted of drunken driving and of persons who warm up their car motors in closed garages in spite of repeated warnings published in newspapers and magazines. For some reason, probably because of mystery stories, radio and television, poisoning is associated with crime, and in the minds of many is the egotistic thought, "It might happen to others but it won't happen to me." And so many absolutely preventable deaths occur.

Personal education can be very effective. It is the physician's duty personally to instruct his patients regarding the many toxic substances about the home, to explain the dangers of carbon monoxide, whatever its source, and to give reasons why a person who has ingested alcoholic beverages should not drive, both for his own safety and for that of others.

While it is neither practical nor, in all probability, proper for a physician to inspect a patient's home to point out potential dangers, he can do much in some general areas. For example, he might give advice such as the following: Empty the medicine cabinet of all partially consumed prescriptions; discard all unlabeled containers, and affix legible labels to all improperly labeled containers; keep poisonous substances in a locked cabinet; do not store insecticides, cresol-containing preparations, etc. on shelves with foodstuffs; label containers of paint and accessories properly and keep them in a locked cabinet; thoroughly inspect the furnace so that carbon monoxide will not wipe out an entire family; repair leaking oil lines and do not permit the oil to drop into a can that is accessible to a child. The list is almost without end. The alert physician will readily recognize other possible sources of accidental poisoning.

Paradoxically, legitimate prescriptions are a common source of poisoning. Unused medications are hoarded and often put to uses never intended by the physician, or the labels may be disfigured or fall off and the material may be mistaken for something else. Children who

see the parents take something from the medicine cabinet are apt to imitate, with sometimes disastrous results. Physicians should not prescribe quantities of medicine greater than necessary for immediate use and should admonish patients to discard all unused material and also that the medicine is for a specific current purpose and must not be used at any subsequent time by anyone. Physicians should thoroughly instruct patients about the possible untoward actions of drugs, particularly barbiturates and other depressing drugs such as codeine, antihistamines and tranquilizers. Patients receiving such medications should not drive a car or work with power machinery and, above all, must keep the drugs out of the reach of children.

People rely on memory and keep such substances as turpentine, kerosene, gasoline, benzene and carbon tetrachloride in vinegar or soft-drink bottles without definitive labels. Too often the original label on the container is retained and because of improper identity serious accidents result. A boy of 13 found a soft-drink bottle with some liquid in it, which he drank; within six hours he was dead. The liquid was a solution of monofluoroacetate.

Another unexplainable habit is the keeping of toxic materials on a shelf with foodstuffs, often in similar containers and unlabeled. A family was wiped out when sodium fluoride stored in a container identical to one containing flour was used to prepare pancakes. Gasoline stored in a vinegar bottle was poured on beets which, unbelievably, were eaten. Pieces of chicken being prepared for frying were shaken in a bag containing a flourlike substance found on the pantry shelf; two persons died from this fantastic use of roach powder.

Naphtha, gasoline and carbon tetrachloride are used in too many homes for cleaning purposes. Besides the possibility of explosion and fire with the first two substances, all three present a real danger in that toxic effects may result from inhalation. While adequate ventilation may protect the user in part, the fumes may become pocketed in another area of the home and effect a toxic reaction on anyone present.

Carbon monoxide, another common poison, is found whenever there is incomplete combustion. Since it is odorless, it insidiously produces its toxic effect. Faulty furnaces, regardless of the type of fuel used, are a constant hazard, and a complaint of headache occurring during the heating season should awaken a consideration of possible carbon monoxide poisoning.

It must be emphasized that it is not sufficient to store household products containing toxic substances on an open shelf, no matter how apparently inaccessible it may seem. A three year old child climbed up on a car in a garage, reached a shelf very high from the floor, and obtained a can of paint containing white lead and proceeded to hand paint himself. Fortunately the consequences were not serious, but this actual happening pinpoints the fact that locked cabinets are the only reasonable safeguard for toxic household items.

Physicians must realize that lay persons do not know, nor should they be expected to know, that many household items are potentially dangerous to health. Further, it is not commercially practical, and probably not desirable, to label many products as poisonous. It may be assumed that many people do not read labels, and if too many labels carried a skull and crossbones and the word "poison," many persons might become indifferent to a multitude of warnings. Thus there are many things a physician can do in advising his patients how to prevent accidental poisoning.

Diagnosis of Poisoning

Diagnosis of poisoning in many cases rests entirely on the history, since many toxic substances do not produce pathognomonic signs or symptoms. Ingestion of corrosive substances usually is indicated by burns or destruction of tissue in the oral cavity and about the mouth. Carbon monoxide effects a cherry-red color to the skin. A stippled black line along the margin of the gums suggests chronic intoxication with heavy metal—lead, mercury, bismuth; it is not present in edentulous persons and may not be marked if excellent oral hygiene is practiced. Constricted pupils are seen in intoxication due to opium, opium derivatives, opiumlike drugs, barbiturates and

anticholinesterase insecticides. A test dose of NALLINE®, 5 mg., will tend to arouse a patient depressed by a drug of the opium group but is ineffective in barbiturate intoxication.

If a history, past and present, is not obtainable, the physician must use his powers of observation. Inspection of the patient and his surroundings is of paramount importance. A container near the patient may suggest a possible source of poisoning, and of course it may be equally misleading and confusing. One should not forget that the patient's condition may be due to disease. It is just as unfortunate to misdiagnose a disease in favor of a poisoning as it is to mistake a case of intoxication for a pathologic condition. Many cases of chronic intoxication require exceptional diagnostic acumen; a few brown spots on the skin did lead a physician to suspect arsenic intoxication after the patient had been to several doctors and a reputable clinic without obtaining a diagnosis for her rather indefinite symptoms.

In many cases, but not in all, the analytic toxicologist may be of considerable help in the diagnosis. The physician should furnish the toxicologist with the history of the case and a description of the symptoms and signs. Since the metabolic products of many of the newer drugs are not known, it is not always possible for the analytic chemist to give a definitive report on such specimens.

Specimens for analysis are limited to stomach contents, vomitus, stomach washings, urine, blood, saliva, spinal fluid and feces. Each specimen should be placed in a chemically clean container, preferably one not used before. Plastic bags are excellent because there is no danger of breakage or contamination. Paper containers such as are used to store foods in a freezer are also acceptable. Each container should be clearly marked and sealed, for there is always the possibility of a criminal or civil suit and the chain of evidence should not be subject to attack. Liquid specimens must be kept refrigerated; solid specimens may be frozen to preserve them. Do not use a preservative!

Other than the corrosive poisons, substances found in the stomach contents, vomitus or gastric washings furnish presumptive evidence only that the patient's condition is due to the material found, since the latter has not been absorbed and actually has not acted on the body. Conversely these specimens may furnish no evidence whatsoever. A case in point is that of a morphine addict who swallowed 12 capsules of pentobarbital of 100 mg. each. Gastric washings 15 minutes later failed to show the presence of barbiturate. After a three hour sleep the patient volunteered the information that this was a customary dose of barbiturate when heroin was not available and that he had had a gastroenterostomy, which apparently permitted the drug to pass quickly beyond the range of the stomach tube. In a case of suicide, a large amount of arsenic was found in the stomach contents but none was found in the tissues; death actually was due to cyanide that had been taken with the arsenic.

Blood samples should be oxalated or treated with sodium fluoride except when a determination of lead is desired. Oil or liquid petrolatum should not be used to cover the blood. The container should be completely filled, without air space. This is particularly important if a volatile substance is being sought. After a paraffined cork is inserted into the container, the cork-container border should be sealed with paraffin or wax. Never permit the blood to freeze. If some time is to elapse before delivery of the blood to the chemist, sodium fluoride is the anticoagulant of choice. Unless thorough drying is permitted, alcohol or ether should not be used to clean the skin over a vein, nor should the syringe and needle be rinsed with these solvents if an analysis for alcohol is contemplated.

Substances found in urine, other than therapeutic agents instilled into the genitourinary system, can be said to have been absorbed into and distributed throughout the body and excreted by the kidneys. The patient's condition is probably but not absolutely due to the substance found. Some poisons either are not excreted by the kidneys or undergo metabolic degradation into products not known at present, and hence an analysis of the urine may be fruitless.

Many times a quantitative analysis of the urine is unwarranted because the function of the kidneys, liver or other organs of detoxication or degradation is not known and cannot be assumed to be normal. However, quantitative analysis of a 24 hour urine specimen is imperative if such poisons as arsenic, lead and mercury are being considered, since these substances are found normally. It is highly important to know if the quantity found is more than the average normal amount. Only then should one attempt to correlate the condition of the patient with the substance found.

For qualitative analysis a spot sample of urine will suffice, but for quantitative examination a 24 hour specimen must be submitted. Clean containers must be used, and if a heavy metal is being sought one must use Pyrex glassware that has been thoroughly cleaned and then rinsed with dilute nitric acid. Since arsenic and lead are ubiquitous, one must take care to prevent contamination of the specimen with dust or other extraneous material. Too often, carelessness in collection negates the value of such a specimen.

Ordinarily a preservative for the urine is not desirable. If a specimen is to be examined shortly after collection, a preservative should not be used. If there is to be a long delay between collection and examination, the physician should contact the toxicologist in regard to the use of a preservative. In any event, the urine should be refrigerated as much as possible but not permitted to freeze. Incidentally, it is not necessary to submit the entire 24 hour specimen. An aliquot suffices in many cases, since the report is based on the quantity of noxious material in a liter of urine. This is a convenience when the specimen must be shipped. The stopper must be securely held in place. Vermiculite is an excellent packing material to protect specimens in shipping, but as a safety measure the container should be enclosed in a plastic bag that is securely and tightly sealed.

The toxicologist's report to a physician or pathologist may merely state that no common poison was found or that analysis was negative for a specified substance. The quantity of lead found in urine is reported as micrograms per liter, the upper level of normal being taken as 80 μg. Alcohol in blood is reported either as milligrams per cent or as per cent. "Milligrams per cent" is to be interpreted as milligrams per 100 ml. (or grams, the difference usually is insignificant) of blood. It is generally accepted that up to 50 mg. per cent (equivalent to 0.05 per cent) of alcohol in the blood is not significant, that between 50 and 150 mg. per cent (0.05 to 0.15 per cent) may indicate that the person is under the influence of alcohol, and that above 150 mg. per cent the person may be presumed to be under the influence of alcohol. The amount of poison found in tissue usually is reported as milligram or microgram per cent, i.e., per 100 gm. of tissue. The toxicologist should be in a position to give the physician an interpretation of chemical findings. It may be necessary to alter the treatment on the basis of the toxicologist's report.

Treatment of Poisoning

Treatment of poisoning is fundamentally that of any other condition. The cardinal principle is to separate the patient from the noxious substance or to render the poison innocuous by destruction, neutralization or some physical means.

If the poison has been ingested it must be removed from the body by inducing vomiting, use of a stomach tube, or catharsis. Renal function must be maintained to aid in excretion of absorbed poison. Diuresis may be of considerable help in preventing nephrosis in instances of poisoning due to such substances as carbon tetrachloride and mercury. Antidotes may be used for their local or systemic effect. If the noxious material has been in contact with the skin or mucous membrane, flooding the area with copious quantities of water is paramount.

There are no hard and fast rules for treatment of any particular case of poisoning. The condition of the patient and the circumstances of the poisoning are the only reliable indexes for treatment, since basically symptomatic treatment must be followed.

The patient should be removed from an atmosphere containing noxious vapors; and this

may suffice, as in cases of mild exposure to carbon monoxide or smoke. If asphyxia is marked, administration of oxygen alone or with 5 per cent carbon dioxide may be indicated. Artificial respiration with or without the insertion of an airway may be required. Even if the patient regains consciousness rather quickly, bed rest for 24 hours is imperative to prevent cardiovascular collapse. One should remember that with a prolonged exposure a comatose condition may continue even after all the carbon monoxide has been removed from the hemoglobin; this indicates definite brain damage and, if awakening does occur, amnesia may be present for months.

If an irritant such as ammonia has been inhaled, extreme care must be taken to protect the lungs from additional mechanical damage since the ammonia has already effected a destruction of pulmonary epithelium. The effect in the lungs of some substances, such as carbon tetrachloride, is secondary to that which the substance may have on the kidneys, heart and liver.

If a corrosive substance has been splashed on the skin or has come in contact with mucous membrane, the area must be flooded immediately with copious quantities of water. It is important to start the lavage as soon as possible to dilute the corrosive and decrease its tissue-destroying action which may in a very short time effect a disabling disfigurement. One should not wait to use more "specific" solvents. What water lacks as a specific solvent it gains in being a general solvent, since all corrosives and irritants are somewhat soluble in water. In addition, a large quantity of water obviously will dissolve a greater quantity of poison than will a small amount of a specific solvent, and the danger of absorption is decreased. The marked increase of temperature which occurs when acid or alkali is mixed with water is dissipated by the large amount of water used.

Whether or not one should induce vomiting when a poison has been ingested is debatable. Of course it is not ever done if the patient is depressed, since aspiration of vomitus almost certainly would occur. One may argue that if a corrosive substance has been taken, vomiting will subject the patient to a second assault of the poison and conceivably could effect a rupture of the stomach or esophagus. In any event one should not assume that the stomach has been emptied of the noxious substance by emesis. Vomitus should be saved for inspection and chemical analysis, and the physician should note its color and odor; very often these characteristics identify the poison. Again we must conclude that the proper treatment is that indicated in the best judgment of the physician.

Use of a tube to remove material from the stomach is another controversial procedure. Due consideration must be given to the danger of perforation of the esophagus or stomach, and it is of prime importance to withdraw the tube in such a fashion that material cannot enter the pulmonary tree. Since aspiration pneumonia is preventable, the physician must take every possible precaution to protect the patient fully from such a consequence. To wash the stomach, it is imperative that small quantities of water or saline solution be used repeatedly. Large amounts may wash the material into the duodenum. Aspiration of stomach contents through a multiple-opening large-bore tube is of unquestioned value. Forceful washing of the stomach is not without danger.

"What is the antidote?" That is one of the most common questions asked of a toxicologist. Antidotes appear to have a halo of omnipotence, but, just as with other therapeutic agents, there is no antidote effective in all cases. Whether the antidote is physiologic, chemical or physical in action, not one can be relied on conclusively to render the poison inactive. Of a certainty, treatment consists of more than just using an antidote.

The so-called universal antidote, which consists of tannic acid, magnesium oxide and activated charcoal, must be mixed with water. Theoretically it is supposed to neutralize acids, precipitate metals and alkaloids, and adsorb many toxic substances. The antidote must be removed; if permitted to remain in the gastrointestinal tract, the complexes formed will be dissociated with liberation of the poison. The charcoal must be activated; inacti-

vated charcoal has little or no adsorbing power. After administration of universal antidote, the stomach should be washed with small quantities of water until the return is practically clear. The input and return should be measured and the amount recorded. If thought necessary, teaspoon to tablespoon quantities of universal antidote suspended in water may be given repeatedly, provided the stomach is washed each time.

The value of dilute oxidizing substances such as 1:5000 and 1:10,000 potassium permanganate is debatable. Under no circumstances is the stomach to be considered similar to a glass test tube. While permanganate may well oxidize and destroy morphine and other toxic material in a test tube, there is no guarantee that this same reaction will occur in the stomach, since the reaction is not specific and the permanganate will be reduced by any organic material. If it is used, the stomach should be washed with water until the return is free of purple color or brown particles.

Overdosage of barbiturates is a too common occurrence. In spite of its frequency, treatment of the condition is most controversial. It is my experience that barbiturates effect an "all or none" lethal action. If the patient is protected against pulmonary infection and if adequate ventilation is provided, he will be on the road to recovery providing too large a dose has not been taken. It should be admitted that METRAZOL® may act as a prognostic drug. If the patient responds to an intravenous dose of 300 mg., recovery is most probable. Megimide may be used to improve respiration, but it does not necessarily arouse the patient from coma. As with other conditions, overtreatment is to be deprecated. It should be mentioned that all barbiturates taken in overdosage are excreted by the kidneys and appear in the urine, from which any one may be extracted and identified. Diuresis does not hasten their excretion. For any patient markedly depressed by a barbiturate or any other drug, the anesthesiologist is best equipped to carry out the necessary procedures, since in fact the depression indicates a deep stage of anesthesia.

Summary

Cases of intoxication due to chemical substances are increasing at a rather alarming rate. The majority of such incidents are preventable. Physicians must be alert to recognize poisonings from chemical substances and differentiate them from intoxications of other origins.

Basically the treatment of poisoning is that of other pathologic conditions. While the initial procedure is separation of the patient from the poison, for the most part treatment is symptomatic. Antidotes may be used with discretion, but full reliance cannot be put on any particular antidote, since none is 100 per cent effective.

Physicians should educate their patients individually about the dangers of toxic substances, and in particular should point out the sources of accidents in the home and suggest corrective measures. A large majority of these poisonings are preventable. The physician must be interested in preventive toxicology. He should become thoroughly acquainted with the procedures of Poison Control Centers and inform his patients of their existence and how to contact such a center in an emergency when the physician may not be available.

Insecticides, Rodenticides, Herbicides; Household Hazards

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DURING the past decade it has become increasingly apparent that the use of chemical agents to control insects and rodents can markedly increase the yield of food crops. Chemical control of weeds also has become an important aspect of modern agriculture. Since 1940 a whole new group of agricultural chemicals has been introduced, enabling farmers to control many more crop-destroying insects, diseases and weeds than ever before. As a result the yields of food crops per acre have reached new high levels. These advances are essential, because we lose approximately a million acres of agricultural land annually in this country to expanding urban and suburban uses. Furthermore, the rapid increase in population insures a greater demand for agricultural products. New pesticides are also being used with great success in the control of disease-carrying insects. It has been estimated that during the past 15 years the use of insecticides has resulted in the saving of five million lives and the prevention of 100 million illnesses in this country.

The general acceptance of the use of pesticides in agriculture and in the home and the recognition of their necessity have perhaps been responsible for frequent neglect of their toxicity to man and domestic animals. To aid in prevention of poisoning by these chemical agents, federal and state legislation has been enacted. The Federal Insecticide, Fungicide and Rodenticide Act of 1947 requires the registration and proper labeling of every new pesticidal agent before it is shipped in interstate commerce. The Miller Pesticide Amendment to the Federal Food, Drug and Cosmetic Act provides for the establishment of tolerance levels for pesticidal residues (the maximal quantities which can be present) on raw agricultural commodities. These levels are established through animal experimentation and

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TABLE 1

ACUTE TOXICITY TO MAN OF SOME INORGANIC INSECTICIDES

COMMON NAME	CHEMICAL NAME	ESTIMATED FATAL ORAL DOSE (GRAMS PER 70 KG.)	ANTIDOTE
Sodium fluoride	Sodium fluoride	1.0	
Arsenic trioxide	Arsenic trioxide	0.1	Dimercaprol
Paris green	Copper acetoarsenite	0.1	Dimercaprol
Tartar emetic	Antimony potassium tartrate	0.15	Dimercaprol
Corrosive sublimate	Mercuric chloride	0.07	Dimercaprol
Borax	Sodium borate	8.0	
Sodium selenate	Sodium selenate	0.2	
Hydrogen cyanide	Cyanide	0.3	Sodium nitrite and sodium thiosulfate

are considerably lower than the levels that cause detectable injury as evidenced by gross behavior, histologic examination of tissues or biochemical analyses.

Most states have legislation concerning pesticides, generally requiring the licensing of each substance before it can be sold. State laws usually follow the same pattern as the federal laws to avoid conflict with respect to labeling. However, uniformity is needed in state laws, because at present the requirements differ greatly in various states. Through state legislation it is possible to regulate the application and use of materials by licensing firms and individuals who dispense and apply toxic chemical agents. Enforcement of state and federal regulations concerning the use of these agents assures the user of the materials of adequate directions and precautions to prevent accidental poisoning, and insures the consumer that dangerous quantities will not remain on food crops. Nevertheless, some of the pesticides have caused a considerable number of accidents through carelessness by those permitted to use them, with the result that poisoning of themselves or others has occurred rather frequently.

Unfortunately, children often are the victims when toxic chemical agents are stored in accessible places. In view of the rapid increase in use of toxic pesticidal chemicals, prevention of accidental poisoning through proper handling and storage is of primary importance. Acquisition of knowledge concerning the symptoms of poisoning and the recommended methods of treatment are now important phases of the education of practicing physicians, who, in addition to handling the medical problems these agents present, are in an excellent position to educate the public in regard to the hazards and benefits of pesticidal agents. I shall describe the toxicity, pharmacologic effects and methods of prevention and treatment of accidental poisoning by the insecticides, rodenticides and herbicides that are of greatest importance and usefulness at present.

Insecticides

Insecticides constitute the largest and most valuable group of chemicals used for pest control. Chemically we may divide the important insecticides into three major groups: inorganic, synthetic organic and botanic. Since there are many species differences in susceptibility to various insecticides, the availability of agents having different modes of toxic action is essential to control the existing wide variety of destructive insects. In addition, development of resistant strains of insects has become a problem of considerable importance, necessitating substitutes whenever a particular species becomes resistant to a chemical agent. Thus a variety of effective insecticidal materials is necessary just as a variety of anti-

TABLE 2

ESTIMATED LETHAL DOSES OF CHLORINATED HYDROCARBON INSECTICIDES

COMMON NAME	CHEMICAL NAME	ESTIMATED FATAL ORAL DOSE (MILLIGRAMS PER 70 KG.)	TREATMENT
Chlorophenothane; DDT	Trichloro-bis (p-chlorophenyl) ethane	30	Phenobarbital
Toxaphene	Chlorinated camphene	5	Phenobarbital
Benzene hexachloride	Hexachlorocyclohexane	28	Phenobarbital
Lindane	Gamma isomer of benzene hexachloride	15	Phenobarbital
Chlordan	Octachloro-hexahydro-methanoindene	6-60	Phenobarbital
Aldrin	Hexachloro-hexahydro-dimethanonaphthalene	5	Phenobarbital
Dieldrin	Hexachloro-epoxy-octahydro-dimethanonaphthalene	5	Phenobarbital
Methoxychlor	Trichloro-bis (p-methoxyphenyl) ethane	350	

biotics and other therapeutic agents to which resistance can develop is necessary. Further, from the economic standpoint the availability of several competing chemicals capable of eradicating various destructive insects is advantageous. From the medical standpoint it is fortunate that individual members of the major classes of organic insecticides produce similar pharmacologic effects in man and domestic animals. In many instances the toxicity of individual members of each class to mammals is within the same range.

Inorganic insecticides—Inorganic insecticides are comparatively simple compounds, generally rather toxic to mammals. Compounds of arsenic and fluorine are the most extensively employed substances, although inorganic salts of antimony, boron, mercury, selenium, cyanide and sulfur also have insecticidal uses. These materials commonly are employed as aqueous sprays and dusts and sometimes are used in sweetened baits.

Table 1 lists the common inorganic insecticides containing the aforementioned metals, together with the estimated lethal doses for man and the specific antidotes when these are available. Among the compounds listed, the arsenicals, mercurials and cyanide are outstanding in their toxicity. Fortunately, effective specific antidotes are available for these substances. The remarkable ability of dimercaprol (2,3-dimercaptopropanol; BAL) to reverse the biochemical combination of arsenic, mercury and antimony with tissue constituents represents a major advance in the specific therapy of metal poisoning. The efficacy of nitrite and thiosulfate in the treatment of cyanide poisoning has greatly reduced the number of deaths from this poison. Details of administration of these antidotes and their effectiveness have been described in numerous published articles and recent editions of textbooks of pharmacology and toxicology. Although the inorganic insecticides have a high toxicity to mammals, both the medical profession and the public are well aware of the hazards associated with their use and this knowledge undoubtedly has resulted in a significant reduction in the number of cases of accidental poisoning.

Chlorinated hydrocarbon insecticides—The chemical prototype for the chlorinated hydrocarbon insecticides is chlorophenothane (DDT®). Although DDT continues to be the compound most extensively used for agricultural and public health purposes, other chlorinated hydrocarbons have become important economically throughout the world and are widely used. The most common agents in this group are aldrin, benzene hexachloride, chlordan, dieldrin, lindane, methoxychlor, TOXAPHENE® and DDD (dichlorodiphenyldichloroethane). Individual members of this class of compounds exhibit differences in chemical

configuration and physiologic actions but their effects on mammals are essentially the same from the clinical standpoint and they can therefore be described as a group.

The chlorinated hydrocarbons are toxic to insects, fish and mammals. Table 2 gives the estimated lethal doses for man of several of these compounds. Intoxication may occur by absorption through the intact skin, by ingestion, or by inhalation. The toxicity by these various routes of administration is influenced by the form in which the compound is dispersed. In this connection, solutions of chlorinated hydrocarbons in mineral oil or organic solvents are available, such as kerosene, emulsion concentrates diluted with water prior to use, powders incorporated in suitable dry carriers, aerosols in oils for dispersion as mists and fogs, and coverings in paints, dishes and waxes. The ability of the chlorinated hydrocarbons to produce injury varies with the type of exposure, the formulation and method of application, and the frequency, amount and duration of contact. Single exposures to relatively large amounts of the compounds and frequent successive exposures to small quantities can cause poisoning, although from a practical standpoint subacute and chronic poisonings are of greatest importance.

Acute poisoning from chlorinated hydrocarbon insecticides produces signs referable to the stimulation of the central nervous system. Hyperexcitability, nervousness, restlessness, muscular spasm and lack of coordination are early signs of intoxication. Salivation, nausea and vomiting may precede the neurologic effects if the compounds have been ingested. Muscle spasms increase in frequency and intensity and progress to convulsions. Convulsions of a tonic and clonic nature are characteristic of poisoning by DDT, aldrin, dieldrin and lindane. Generalized epileptiform convulsions are the most prominent feature of Toxaphene poisoning. The immediate cause of death in most cases is respiratory failure but it may be ventricular fibrillation; chlorinated hydrocarbons sensitize the heart to injected and endogenous epinephrine and thus induce ventricular fibrillation.

Symptoms of subacute poisoning by the chlorinated hydrocarbon insecticides are loss of appetite and weight, emaciation, hyperirritability, tremors, convulsions and coma. The liver may enlarge, and cellular degeneration of liver, kidney and brain is noted. Chronic poisoning by the chlorinated hydrocarbons produces similar effects. However, dietary levels which do not produce symptoms may cause moderate enlargement of the liver, minor nonspecific hepatocellular alterations, and a change in the estrus cycle in females. The chlorinated hydrocarbons are stored in the body fat, and the amount stored varies with the particular insecticide, the amount of fat in the body, and the rate of administration. Some compounds are stored in their original forms; others accumulate as metabolites of greater or lesser toxicity than the original compounds.

A number of studies of the chronic effects of chlorinated hydrocarbons have been conducted on experimental animals, but it is not known whether these agents have a higher toxicity when they are present in the diet of man, which contains coloring agents, preservatives and a number of other food additives and contaminants. Many drugs, food additives and contaminants utilize common detoxication pathways, and it is possible that the detoxication systems in man might be less able to handle a particular compound in the presence of other chemicals than are the detoxication systems in experimental animals receiving diets free from these other substances. It is difficult experimentally to test the chronic toxicity of chemical agents under more realistic conditions with respect to possible interfering substances. We should recognize the limitations of the present procedures for testing chronic toxicity and consider possible practical methods of obtaining a realistic evaluation of chronic toxicity as a worthwhile area of research in toxicology.

With respect to diagnosis of poisoning by the chlorinated hydrocarbons, one may anticipate the same physiologic reactions in humans as those observed in animals. However, the presence of illness together with a history of exposure to the insecticide may be misleading. For poisoning to occur, the compounds

must be used in such a way as to permit excessive absorption. When they are used according to the manufacturer's recommendations there ordinarily is no health hazard. Symptoms must be of the type that may be expected from chlorinated hydrocarbons. It is apparent that the early manifestations of poisoning such as headache, nausea, vomiting, hyperirritability, weight loss and convulsions can occur in a variety of systemic illnesses. Thus it is important to examine the patient carefully and exclude other diseases. Absence of fever and changes in blood counts and blood chemistry and the presence of diffuse cortical discharges in the electroencephalogram constitute differentiating evidence of poisoning by chlorinated hydrocarbons. Disappearance of symptoms within a month or two after the cessation of exposure constitutes additional evidence of poisoning by these insecticides.

Treatment of poisoning by chlorinated hydrocarbon insecticides is largely symptomatic and supportive. Of primary importance is removal of the patient from further exposure in chemical industry, during field application of the materials, in the home, or wherever the exposure has occurred. Mild symptoms referable to stimulation of the central nervous system can be treated by small oral divided doses of phenobarbital. Severe intoxication which causes convulsions should be treated by parenterally administered barbiturates. Initially, thiopental sodium may be given by vein followed by phenobarbital sodium intramuscularly until convulsions are controlled. Two recent articles[1,2] provide additional information on the toxicity and treatment of poisoning by chlorinated hydrocarbon insecticides.

Organic phosphorus-containing insecticides—The insecticidal activity of certain organic esters of phosphoric acid was discovered by Schrader in Germany about 20 years ago. Extensive research on the toxicology and pharmacology of insecticidal organic phosphates has been conducted in this country since 1947 when they were first employed in agriculture. This group of compounds has come into widespread use throughout the world for eradication of destructive insects. The continued development of new compounds belonging to this class is evidence of their effectiveness in this regard.

The first organic phosphate employed extensively as an insecticide on food crops in this country was parathion (diethyl-p-nitrophenyl monothiophosphate), a relatively simple ester of thiophosphoric acid. It still is widely used. At present, use of the following organic phosphates on food crops is permitted by the Departments of Agriculture and Health, Education and Welfare: methyl parathion, malathion, systox, diazinon, guthion, trithion and EPN (ethyl-p-nitrophenyl thionobenzenephosphonate). For each, a maximal level (tolerance) which can be present in food was carefully established by animal experimentation before the compound was introduced into practical use. Table 3 summarizes the tolerance levels and data on the acute toxicity of these compounds.

A number of other organic phosphates are under development for use as agricultural insecticides or are already in use for eradication of insects other than those which affect food crops. Table 4 summarizes the toxicity of several of these compounds.

Most of the insecticidal organic phosphates have a high mammalian toxicity (tables 3 and 4). A few, including malathion and dipterex, have low toxicity to man and domestic animals, due apparently, at least in part, to rapid detoxication. Most of the organic phosphates are readily absorbed from the skin, lungs and gastrointestinal tract, thus increasing the possibility of acute poisoning during their application and use.

Until recently it was assumed that combinations of organic phosphates would have additive toxic effects because they all have the same mechanism of action. However, recent research[3] in the laboratories of the Division of Pharmacology of the Food and Drug Administration has shown that greater than additive toxicity results from the simultaneous administration of EPN and malathion to animals. Potentiation of toxicity occurred both when acutely toxic doses were administered and when low levels of the compounds were added to the diet. This finding has consider-

TABLE 3

ACUTE TOXICITY AND TOLERANCE LEVELS OF ORGANIC PHOSPHORUS-CONTAINING INSECTICIDES

COMMON NAME	CHEMICAL NAME	ESTIMATED FATAL ORAL DOSE (GRAMS PER 70 KG.)	TOLERANCE LEVEL (PARTS PER MILLION)
Parathion	Diethyl-p-nitrophenyl monothiophosphate	0.1	1.0
Methyl parathion	Dimethyl-p-nitrophenyl thionophosphate	0.15	1.0
Malathion	Dimethyl S-(1,2-bis-carboethoxy) ethyl phosphorodithioate	60.0	8.0
Systox	Diethyl-0-ethylmercapto-ethyl phosphorothioate	0.1	0.75
EPN	Ethyl-p-nitrophenyl thionobenzenephosphonate	0.3	3.0
Guthion	Dimethyl S-(4-oxo-1,2,3-benzotriazinyl-3-methyl) phosphorodithioate	0.2	2.0
Diazinon	Diethyl 0-(2-isopropyl-6-methyl-4-pyrimidyl) phosphorothioate	25.0	0.75
Trithion	S-(p-chlorophenylthio)-methyl-0,0-diethyl phosphorodithioate	0.6	0.8

TABLE 4

ACUTE TOXICITY OF ORGANIC PHOSPHORUS-CONTAINING INSECTICIDES

COMMON NAME	CHEMICAL NAME	COMPARATIVE TOXICITY	ESTIMATED FATAL ORAL DOSE (GRAMS PER 70 KG.)
TEPP	Tetraethylpyrophosphate	Highly toxic	0.05
OMPA	Octamethyl pyrophosphoramide	Highly toxic	0.2
Dipterex	Dimethyl-1-hydroxy-2,2,2-trichlorethylphosphonate	Moderately toxic	25.0
Chlorthion	p-Nitro-m-chlorophenyl dimethylthionophosphate	Slightly toxic	60.0
Di-syston	Diethyl-S-2-ethyl-2-mercaptoethyl phosphorodithioate	Highly toxic	0.2
Co-ral	Diethyl-0-(3-chloro-4-methyl-7-coumarinyl) phosphorothioate	Moderately toxic	10.0
Delnav	2,3-p-dioxanedithiol S,S-bis (0,0-diethyl phosphorodithioate)	Moderately toxic	5.0
Phosdrin	Dimethyl-0-(1-methyl-2-carbomethoxyvinyl) phosphate	Highly toxic	0.15

able practical importance, because the diet of man could contain both these agents. Recent experiments by Cook and associates[4] and by Murphy and DuBois[5] have shown that the feeding of low dietary levels of EPN inhibits an enzyme in the liver and some other tissues which catalyzes the hydrolytic detoxication of malathion. It appears that the same enzyme catalyzes the detoxication of ester-type drugs. Thus, inhibition of this enzyme by the ingestion of food contaminated with EPN could result in abnormal susceptibility to the toxic effects of some of the common drugs. It is not yet known whether the interference by EPN with drug detoxication presents a health hazard to consumers of insecticide-treated foods. However, the demonstration that this insecticide can interfere with detoxication of other chemical agents foreign to the body suggests that more attention should be given to a study

of the metabolic pathways involved in detoxication of chemical agents with the understanding that food additives, pesticides and therapeutic agents containing similar chemical groups and linkages can be expected to utilize common pathways.

All the organic phosphorus-containing insecticides have essentially the same mechanism of action. They owe their toxicity to an ability to inhibit cholinesterase, the enzyme that normally detoxifies acetylcholine. Some organic phosphates undergo metabolic conversion to yield cholinergic metabolites. Thus the insecticidal thiophosphates undergo metabolic change in the liver which consists of the replacement of sulfur by oxygen. The resulting oxygen analogue is the inhibitor of cholinesterase. The end result of the inhibition of cholinesterase activity is accumulation of acetylcholine. The resulting symptoms resemble those that one would expect from excessive and continued stimulation of the central nervous system and structures innervated by the parasympathetic and somatic motor nerves. The clinical manifestations of poisoning consist of weakness, unsteadiness, blurred vision, headache and nausea. These symptoms are followed by vomiting, abdominal cramps, diarrhea, salivation, lacrimation, profuse sweating, tremors of the extremities, and difficulty in breathing. Pinpoint and nonreactive pupils are observed, and secretions accumulate in the respiratory passages. Cyanosis may occur as well as severe muscular fibrillations, coma and convulsions. Death is associated with respiratory failure. After lethal doses the onset of symptoms usually is extremely rapid and death generally occurs within 24 hours. After sublethal doses, reversal of the inhibition of cholinesterase and disappearance of the symptoms occur, but the rate varies from a few hours to several days with different compounds.

The medical aspects of poisoning by insecticidal organic phosphates consist of prevention, detection and treatment. Prevention can be accomplished by education of persons occupationally exposed to the compounds concerning the dangers of skin contamination, inhalation and ingestion. Protective clothing should be worn, and contaminated skin washed immediately. Detection of poisoning by organic phosphates depends on recognition of the characteristic symptoms of acetylcholine poisoning. Exposure to amounts of organic phosphates too low to produce symptoms can be detected by periodic measurement of blood cholinesterase. Marked depression of the cholinesterase activity of the blood occurs before symptoms appear. It is thus possible to terminate the exposure or institute proper protective measures before poisoning occurs.

The present method of treatment of acute poisoning by organic phosphates consists of supporting respiration and administering atropine. Artificial respiration or the administration of oxygen, when possible, should be maintained as long as signs of respiratory embarrassment persist, and the respiratory tract should be kept clear of secretions. Atropine is the specific antidote for organic phosphate poisoning. The initial dose usually is 2 mg. but in severe cases 4 or 6 mg. can be given. Initially the interval between doses is 15 to 30 minutes and repeated doses are given until full atropinization is obtained. The doses can then be decreased and given less frequently. A total dosage of 20 to 30 mg. usually is required during the first 24 hours. Although atropine has been of great benefit in saving the victims of acute poisoning by organic phosphates, its effectiveness is limited to an ability to counteract about two or three lethal doses. Thus, attempts to prevent poisoning should be continued through education of persons who are occupationally exposed concerning the dangers associated with careless handling and misuse of these chemical agents.

Botanic insecticides—A few substances of botanic origin continue to be used rather extensively for insect control. Except for nicotine, these materials seldom cause serious poisoning. The botanic insecticides most often employed are rotenone, pyrethrins and nicotine. Table 5 summarizes the toxicity of these substances to man.

The ground roots and extracts of the roots of rotenone-bearing plants (derris and *Lonchocarpus*) are used as insecticides. They are prepared as dusts with inert diluents or with other insecticides, as washes and dips against ani-

TABLE 5

TOXICITY OF INSECTICIDES OF BOTANIC ORIGIN TO MAN

COMMON NAME	TOXIC CONSTITUENTS	COMPARATIVE TOXICITY	ESTIMATED FATAL ORAL DOSE (GRAMS PER 70 KG.)
Pyrethrum	Pyrethrins and cinerins	Slightly toxic	50
Derris	Rotenone	Slightly toxic	10-100
Allethrin	Allyl cinerin	Slightly toxic	
Tobacco	Nicotine	Highly toxic	0.07

mal ectoparasites, as agricultural, horticultural and household sprays, as emulsions, lotions and ointments for treatment of head lice scabies, and as a palliative for chigger bites. Local effects reported after exposure to derris have included conjunctivitis, dermatitis, pharyngitis and rhinitis. In the finely divided form it is irritating to the skin of experimental animals, and in the undiluted form it is irritating to the conjunctiva and produces numbness of the mucosa of the nose and throat which persists for several hours. Orally it is a gastrointestinal irritant and produces nausea and vomiting promptly after ingestion. The local effect on the intestinal tract together with a stimulant effect on the emetic center tend to force expulsion of the material before absorption occurs. It is much more toxic when it is inhaled. Treatment of rotenone poisoning is largely symptomatic and supportive and consists of removal of the material from the skin and gastrointestinal tract. Oily cathartics should not be used to aid in the removal of rotenone from the gastrointestinal tract.

Pyrethrum is one of the oldest insecticides known to man. The constituents that are active as insecticides are esters called pyrethrins and cinerins. The ground flowers of the plant are used undiluted or mixed with inert diluents or other insecticides as household and horticultural dusts. Liquid extracts employing kerosene or other organic solvents are used in preparing agricultural, livestock and household sprays. The pyrethrins are slightly sternutatory and without irritating effects on the skin. Pyrethrum dust may produce allergic attacks in persons sensitive to ragweed pollen. Toxic doses produce hyperexcitability, incoordination, tremors, paralysis and death due to respiratory failure. Treatment consists of the removal of the offending agent from the environment and supportive therapy for the asthmatic or dermatologic conditions.

Nicotine salts have long been used for eradication of plant lice. Nicotine, a powerful and rapidly acting poison, stimulates and then depresses the autonomic ganglia and the central nervous system. Death may occur in minutes and is due to a curarelike paralysis of the respiratory muscles. Treatment of nicotine poisoning requires prompt and complete removal of the poison from the skin or stomach and the promotion of respiration.

Rodenticides

The rodenticides in common use are inorganic salts and synthetic and naturally occurring organic compounds. The most prominent inorganic compounds are barium carbonate, thallium sulfate, and zinc phosphide. The most widely used organic compounds are WARFARIN®, sodium fluoroacetate, alphanaphthyl thiourea and strychnine sulfate. Table 6 summarizes the approximate lethal doses of these materials to man.

Thallium is the most dangerous of the inorganic rodenticides. It is used in control of ants and rodents in the form of jelly baits or poisoned seeds. Toxic doses produce severe gastrointestinal symptoms, pain in the extremities, peripheral neuritis, blindness, psychosis, loss of hair, and paralysis of special sense functions. Gastric lavage followed by intravenous administration of 1 gm. of sodium

TABLE 6

ESTIMATED FATAL DOSES OF RODENTICIDES TO MAN

COMMON NAME	CHEMICAL NAME	COMPARATIVE TOXICITY	ESTIMATED FATAL ORAL DOSE (GRAMS PER 70 KG.)	ANTIDOTE
Thallium sulfate	Thallium sulfate	Highly toxic	1	
Barium carbonate	Barium carbonate	Moderately toxic	5	Magnesium sulfate
Strychnine sulfate	Strychnine sulfate	Highly toxic	0.1	Barbiturates
ANTU	Alphanaphthyl thiourea	Slightly toxic	7-10	
1080	Sodium fluoroacetate	Highly toxic	0.15	
Warfarin	Acetonylbenzyl hydroxycoumarin	Slightly toxic	0.5	Menadione sodium bisulfite

thiosulfate several times daily may be of value if an appreciable amount of thallium has not been absorbed.

The toxicity of barium carbonate is rather low by the oral route but it is absorbed to a sufficient extent so that it can cause poisoning. The toxic action of the barium ion results in severe gastrointestinal symptoms, cardiovascular irregularities and respiratory difficulties. Treatment consists of oral administration of magnesium or sodium sulfates to precipitate the barium ion.

Zinc phosphide is not widely used as a rodenticide partly because of its high toxicity and strong odor. Most domestic animals will not touch baits containing zinc phosphide, but rodents seem to like the pungent odor of phosphorus compounds and readily accept baits containing this compound. Inhalation of zinc phosphide dust is followed in several hours by vomiting and diarrhea, cyanosis, rapid and soft pulse, restlessness, fever and albuminuria. Treatment of zinc phosphide poisoning from ingestion consists of removal of the poison by gastric lavage, administration of cathartics and enema.

Organic rodenticides differ widely in their toxicity to mammals. One of the least toxic of this group is red squill. This botanic substance contains cardiac glycosides. On ingestion it is an irritant and central-acting emetic. Purging, abdominal pain, blurred vision, cardiac irregularities, convulsions and death from ventricular fibrillation occur in animals following large amounts of material. Treatment consists of emptying the stomach and administering 0.2 gm. quinidine sulfate orally to reduce myocardial irritability.

Another comparatively safe organic rodenticide is alphanaphthyl thiourea. It is toxic to household pets but its toxicity to humans is apparently fairly low. Pulmonary edema and pleural effusion are the principal changes in acutely poisoned animals. Since the compound is insoluble, gastric lavage is a highly useful countermeasure when the material has been ingested. Postural drainage and administration of oxygen are recommended for management of pulmonary edema.

In the past few years another comparatively safe rodenticide has come into rather extensive use. It is an anticoagulant related to bishydroxycoumarin and is called Warfarin. It produces a reversible and controllable hypoprothrombinemia and capillary injury. Single doses do not produce signs of poisoning but successive small daily doses cause cumulative toxic effects in three or four days. These include weakness, pallor, subcutaneous hemorrhages, oral or rectal bleeding, and death after 12 to 15 days. Warfarin inhibits prothrombin synthesis but the liver contains a sufficient reserve and this inhibition must continue until the reserve is depleted before symptoms appear. Treatment of Warfarin poisoning consists of transfusions of whole blood accom-

panied by slow intravenous administration of massive doses of a soluble form of vitamin K such as menadione sodium bisulfite until the prothrombin time is restored to normal.

The highly toxic organic compounds that are used as rodenticides are sodium fluoroacetate and strychnine sulfate. Fluoroacetate is a highly toxic and a very effective rodenticide. Because of its extreme toxicity to most forms of life and because of the lack of specific antidotes, it is not available for household or general use. It is sold only to licensed pest-control operators and others qualified by training and experience in rodent-control procedures. Sodium fluoroacetate acts predominantly on the heart and the central nervous system. Symptoms following ingestion include excessive salivation, nausea and vomiting, muscular twitching, cardiac irregularities, cyanosis, generalized convulsions and death from ventricular fibrillation or respiratory failure. Symptoms frequently appear soon after ingestion but may be delayed for several hours. There is little evidence for the effectiveness of any treatment for sodium fluoroacetate poisoning in man. Repeated small intravenous doses of a short-acting barbiturate may be required to control convulsions, and slow intravenous injection of procaine amide has been recommended as a measure to restore normal rhythm in ventricular fibrillation.

The high toxicity of rodent baits containing strychnine and this alkaloid's ability to produce marked and localized stimulation of the spinal cord with resultant spinal convulsions of the symmetrical and incoordinate type are well known. The object of therapy in strychnine poisoning is to prevent convulsions and protect the medulla from anoxia and excessive stimulation. By use of central nervous system depressants such as the barbiturates it is possible to antagonize the action of strychnine and abolish completely all abnormal motor activity.

Herbicides

Weed control is accomplished at present by the use of general contact weed killers and selective herbicides. The contact weed killers in common use are sodium chlorate, sodium arsenite, sodium hydroxide, sulfuric acid and petroleum products such as diesel oil and crude oil. Their toxic properties and the recommended treatments have been described in textbooks of pharmacology and medicine. Organic compounds other than petroleum products include salts of pentachlorophenol, dinitrophenols and trichloroacetic acid. Pentachlorophenol is used as a wood preservative for protection against termites, beetles and fungi. It possesses considerable toxicity and is an irritant and convulsant poison which may damage the liver and kidney. Treatment is mainly symptomatic and supportive.

The dinitrophenols are potent metabolic stimulants which can be toxic by inhalation, ingestion or skin absorption. Increased temperature, increased respiration and accelerated cardiac rate, and fever, nausea, profuse sweating and collapse may be expected on absorption of toxic amounts. Oxygen and circulatory stimulants are used in treatment of poisoning by these chemicals.

The selective herbicides or hormone-type weed killers are plant-growth regulators and as a group are relatively nontoxic. They include alphanaphthaleneacetic acid, maleic hydrazide, and chlorinated phenoxyacetic acid (2-4D, 2,4,5 T). Persons sensitive to phenols may experience sensitivity to the phenolic compounds, but otherwise they are nonirritating to the skin except in concentrated form.

Household Hazards

In addition to pesticides and drugs, a number of chemicals ordinarily used in households are known to be inedible but many individuals do not regard them as poisonous. It is beyond the scope of this article to enumerate and discuss even a fraction of these substances. Among the most common offenders are paints, cleaners, cosmetics and miscellaneous agents. There is no federal legislation requiring the labels on these substances to give information concerning composition or hazards arising from their use or misuse. In addition, often the toxic components are not shown on the labels, and this group of chemicals therefore presents some major problems in poisoning. It is extremely important to prevent acciden-

tal poisoning through education and adequate labeling. Continued attention to collection of accurate statistics on morbidity and mortality has encouraged health departments, medical societies and others to undertake protective measures. In this connection one of the most valuable recent developments has been the establishment of poison control centers in a number of major cities in this country. Through these centers, physicians can obtain information concerning the composition of substances involved in poisonings as well as methods of treatment. In turn, physicians can contribute to the knowledge of substances that are accidentally ingested and acquaint parents with home-safety measures.

A great deal of additional cooperative effort between physicians and toxicologists is needed to extend knowledge of the identity and nature of hazardous substances, promote safe labeling and packaging of household chemicals, restrict from the home those substances whose hazardous nature outweighs their usefulness, and educate the public in the safe use and storage of inedible substances.

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1958

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 10-13 Municipal Auditorium Cleveland, Ohio

Detection, Recognition and Management of Anemia

Anemia, whether primary or an aspect of other disease, is invariably detected by a reliable hemoglobin determination. Recognition of the general mechanism of the anemia, whether (1) increased red blood cell loss or destruction or (2) decreased red blood cell or hemoglobin production, is the first step in diagnosis. Thereafter, the specific cause may be defined directly or by exclusion. The appropriate therapy by specific nutrients, hormones, chemotherapy, irradiation and splenectomy will be illustrated.

WILLIAM B. CASTLE, M.D.

George Richards Minot Professor of Medicine, Harvard University; Director, Thorndike Memorial Laboratory; Director, Second and Fourth (Harvard) Medical Services, Boston City Hospital, Boston

General Developments in the Field of Anesthetic Agents

MAX S. SADOVE AND ARTHUR T. SHIMA*

University of Illinois, Chicago

THE specialty of anesthesiology is a dynamic, actively moving, changing field which is quick to look into new things and to abandon the old when it proves wrong, as well as to abandon the new when something better supersedes it. The purpose of this paper is not to discuss in detail recent developments in this specialty but rather to give a cross section of some of them.

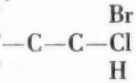
MAX S. SADOVE

ARTHUR T. SHIMA

Inhalation Agents

Research is continuing for new and safer inhalation agents, and chemists have developed quite a number of new drugs. Fluorinated compounds are among those which in general exhibit lower toxicity, high potency, and lack of explosibility.

Fluothane, a halogenated ethane with the chemical formula 2-bromo-2-chloro-1-1-1-trifluoroethane, has just been approved for use in this country.



It is very potent, creating anesthetic states in a range similar to chloroform. It is rapid-acting, nonexplosive and nonirritating to the tracheobronchial tree and gives fair to good relaxation. Early investigations show this compound to hold great promise if one can control the concentration by adequate equipment, thus diminishing potential toxicity. With average hospital equipment it would be too easy to give an overdose. Overdosage produces circulatory and respiratory depression, and visceral toxicity is a potentiality. The next few years should clear up many questions concerning this drug, especially as to hepatic and cardiac toxicity.

Fluomar, a tri-fluoro-ethyl-vinyl ether, is an-

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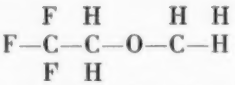
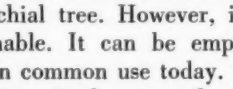
other fluorinated compound being investigated clinically.



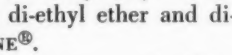
It is more potent than ether, less potent than fluothane, fast in its activity in induction, relatively nontoxic, and nonirritating to the tracheobronchial tree. However, it is potentially flammable. It can be employed with equipment in common use today. Its place is as yet undetermined, primarily because of economic factors.

VINEMAR®, an ethyl-vinyl ether, has properties of both di-ethyl ether and di-vinyl ether or VINETHENE®.



With it, one can induce and maintain anesthesia with a single agent instead of using divinyl ether for induction and di-ethyl ether to maintain anesthesia. It is also useful as a supplement to nitrous oxide, providing a rapid activity base.

There is a "settling down" in the use of TRIMAR® or TRILENE® (trichloroethylene).



It is not used as frequently as a primary anesthetic agent but it is used as a basal or supplemental agent to nitrous oxide in obstetric, dental, orthopedic and neurosurgical procedures and when a nonexplosive technic is desired. The difficulty has been that many have tried to use it as the primary agent. If administered correctly, its toxicity is minimal. However, careless use with soda lime with consequent breakdown of the drug and formation of phosgene has caused complications. Trilene is still being employed as a primary analgesic for obstetrics and at times is combined with nitrous oxide as an anesthetic.

In general, there is a marked decrease in the use of ethyl chloride, Vinethene and similar drugs for induction of anesthesia with the open drop technic. Patients are demanding intravenous or other nonirritating induction agents. Ethyl chloride, due to potential toxicity, is used less and less by anesthesiologists.

The open drop technic, which has been used by countless interns, residents, nurses and anesthesiologists, employing a Yankauer wire mask with either stockinet or many-layered gauze covering, has been shown to cause accumulation of carbon dioxide. The excellent work done at the Mayo Clinic by Faulkner and associates has demonstrated that there is a definite need to insufflate oxygen under the mask. The mask must not have a thick covering; if it does, the carbon dioxide tension is raised and the oxygen tension falls unless oxygen is insufflated. Omission of oxygen insufflation could be hazardous to the poor-risk patient and the very small child.

Lighter planes of anesthesia with ether are being increasingly utilized in this country—not necessarily the degree of lightness popularized by Artusio, but light planes approaching analgesia. In this manner the undesirable effects of ether anesthesia are notedly diminished, especially when one uses one of the balanced anesthesia technics, such as PENTOTHAL® induction with intratracheal technic and curare or curarelike agents for relaxation. It is a common occurrence in the average case with a duration of anesthesia of one and a half to two hours for only about 25 cc. of ether to be volatilized and for most of it to be eliminated within a few minutes of the end of the operation and the patient to awaken without nausea or vomiting.

Use of nitrous oxide has risen markedly, though it is employed less as a sole agent and more in balanced technics, supplemented by narcotics or cyclopropane.

Intravenous Agents

Many new intravenous agents have been and are being synthesized. Basically they have little real advantage over Pentothal (thiopental sodium). More and more inductions of all types of anesthesia are being started with an intravenous agent, which is then continued as the supplemental agent to other technics. Over the years certain points concerning the use of intravenous agents have been established.

1. As larger and larger quantities are used, there is no doubt that emergence is progressively delayed.

2. The agents are so safe that they frequently are used carelessly, thereby causing difficulty or accidents.

3. A common error is failure to determine the patient's requirements by bio-assay, and to administer a fixed amount.

4. Shocked, debilitated, aged and hypovolemic patients require much smaller amounts for induction of anesthesia than those ordinarily required; 50 to 100 mg. is all that may be used by the anesthesiologist for induction. These agents can be given even in the presence of shocklike states by those skilled in their administration, but since the drugs are vasodilators they must be carefully used.

5. The deeper we carry a patient and the more drug we give, the more depression of respiration follows and the more need for assuring adequate respiratory exchange by assisted or controlled respiration.

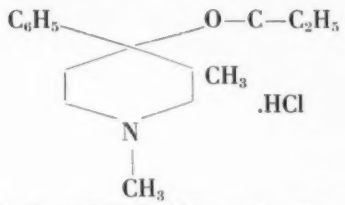
6. Basically the action of the drugs is terminated by their redistribution rather than their metabolic breakdown.

7. Barbiturates are being used less as primary or total agents, but in combined technics are extremely popular.

8. In children, barbiturates given rectally in a dosage of 1 gm. of a 10 per cent solution for a 50 to 75 lb. child, as they are frequently given, will result in a delay in emergence.

Many other compounds are being investigated in regard to maintenance of anesthesia by the intravenous route. VIADRIL® (hydroxydione sodium), an example, is a rather safe, mild steroid capable of producing depression of the central nervous system. It is slower in its action and occasionally more irritating locally, but there seems to be less over-all reflex activity and low toxicity and thus a drug such as this finds usefulness for head and neck surgery and similar operations where vagal reflexes might be a problem. Other agents studied have not reached significant popularity.

In some parts of this country, narcotics given intravenously are finding popularity as supplemental agents; this is especially true of the newer synthetic compounds such as NISENTIL® (1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride).



Anesthesia is induced with an intravenous barbiturate and then maintained with varying concentrations of nitrous oxide (approximately 65 to 75 per cent) and small repeated amounts of the narcotic. One of the more popular methods is the use of DEMEROL® intravenously as an adjunct to nitrous oxide. This method is applied rather extensively in areas where cautery and explosive hazards are a problem. If employed correctly, it is an excellent technic, but in cases of shorter duration it is less efficient than it is in those that last one and a half hours or more. The narcotics produce some respiratory depression, and so many of them are combined with a narcotic antagonist in varying ratios, for example, Demerol-LORFAN®, 80:1 to 100:1; Nisentil-Lorfan, 50:1. Or a narcotic antagonist is given at the end of an operative procedure during which respiratory depression has been offset by assisted respiration.

As long as one uses small intermittent doses of the narcotic there is little difficulty, but when the dose is large or given too fast (more than 20 mg. in a single intravenous injection of Demerol) it is common to see mild hypotension. A great many newer synthetic narcotic drugs are being studied for more specific therapeutic effect with fewer secondary or side effects.

Relaxants

Relaxants are becoming a more integral part of every anesthesia where relaxation is a problem. It is the feeling at this time that when they are correctly used they represent less of a hazard than the use of deeper anesthesia to achieve adequate relaxation.

Succinylcholine (QUELICIN®, ANECTINE®, SUCOSTRIN®, SUXINYL®), the short-acting depolarizing agent, is to a great degree replacing the natural curares. When these agents are properly used there can be little doubt that

many lives are saved, but their improper use is still fraught with hazard, as with any potent compound. In moribund patients or those who are extremely poor risks, relaxants such as succinylcholine are being given to produce an almost ideal operating condition—light anesthesia in planes or concentrations insufficient to cause body derangement. However, there are certain things which we fear and which deserve emphasis since they are not generally known.

When large quantities of relaxants are given, especially with controlled respiration, difficulty in initiating spontaneous respiration is seen. Also, many of these drugs do have a ganglionic blocking effect or at least a peripheral vascular pooling effect. Respiration is depressed and must be assisted. Frequently the physician fails to recognize the respiratory depression because the patient appears to have regained full motor control when residual curarization still is present. Thus an airway is removed too early and the patient is left unguarded or is returned to average floor care instead of remaining in the recovery room, and he may have respiratory difficulty.

A simple check for residual curarization is to ask the patient to squeeze one's hand tightly and maintain the grip, or to open his eyes widely and take a few deep breaths under observation. Failure to do these things is an indication of residual curarization.

This hazard of residual curarization is not adequately appreciated. Means should be at hand to assist respiration and to control the airway wherever relaxants are used.

The anticurare drugs should be administered to patients who have had depolarizing agents only by physicians who are expert in their use, and it is preferred that the patients be watched and given adequate oxygen therapy by the average anesthetist. TENSILON® (edrophonium) and PROSTIGMIN® are useful antagonists with the true blocking-type agents such as the natural curares but are hazardous with depolarization agents such as succinylcholine.

There is a strong feeling among anesthesiologists that whenever relaxants are used respiration is in general inadequate. There is also the feeling that almost all patients, especially those in the Trendelenburg, acute lithotomy, lateral jackknife, or similar respiration-limiting positions, require assistance to respiration. In many instances respiration appears to be adequate when in reality it is dangerously inadequate. Assuring adequate respiration both during and after operation will eliminate the majority of the undesirable effects of the relaxants. There is no substitute for careful, continuous observation.

Spinal Anesthesia

It is unfortunate that use of the excellent technic of spinal anesthesia is diminishing primarily because of foolish, unscientific fears of medicolegal repercussion. Careful studies by groups who have used spinal anesthesia in large numbers of patients have shown that the incidence of complications is lower than it is with many general technics. Use of the catheter and plastic tubing in continuous spinal technic has greatly increased the versatility and usefulness of spinal anesthesia. There has not been a significant increase in complications using these continuous or intermittent technics. The weighting substances such as dextrose and vasoconstricting compounds (epinephrine or NEO-SYNEPHRINE®), when used with proper precautions, have markedly increased the usefulness of the single "shot" spinal by increasing the duration. However, although in skilled hands they widen the scope of spinal anesthesia, in unskilled hands they may increase the dangers.

A great danger of spinal anesthesia still resides in that group of cases in which the surgeon is his own anesthetist and in which the level of anesthesia is not continuously monitored and the physiologic results are not continuously observed. There should be no real difference between spinal and general anesthesia. Both require careful and continuous observation.

Just as with other forms of anesthesia, newer agents are being utilized by various groups for spinal anesthesia. The agents have specific advantages and disadvantages; for example, lucaine (B [2 piperidyl] ethyl orthoaminobenzoate hydrochloride), a piperidine deriva-

tive, has a somewhat sparing action on motor components and therefore may be indicated in certain pelvic and other operations in which motor power and lack of muscular depression are advantageous.

Regional Anesthesia

With more and more anesthesiologists becoming skilled in the use of regional technics, this valuable method of anesthesia is increasing in its usefulness, especially in the many specific anesthetic problems. Probably one of the best examples is the growing utilization of single administration and intermittent or continuous epidural anesthesia. This valuable approach is justifiably increasing in use, especially since many newer agents are being made available which are more potent and potentially less toxic clinically. Some of these are of short duration and low toxicity, such as 2-chlor procaine. Others of greater potency are CYCLAINE® (1-cyclohexylamino-2-propyl benzoate hydrochloride) and XYLOCAINE® (lidocaine hydrochloride). Mixtures of these products with standard agents such as PONTOCAINE® (tetracaine) are enabling the anesthesiologist to utilize technics with extremely low systemic toxicity while making available almost ideal operating conditions.

This valuable method should be more widely taught and applied. If one takes the trouble to learn the technic and its hazards, it has a great deal to offer the surgeon and the patient and can be applied to a wide variety of conditions and states, not only for anesthesia but also for control of pain, treatment of vasospasm, and so on. It could be extremely valuable in a major civilian disaster because of its simplicity and ease of application and also because little equipment is needed and the method has wide applicability.

Tranquilizers

In the past few years many agents which are primarily tranquilizers have become part of the anesthesiologist's armamentarium in order to create a state of indifference, quiescence, amnesia or even sleep prior to anesthesia. Examples are THORAZINE® (chlorpromazine), PHENERGAN® (promethazine), SPARINE® (promazine), PACATAL® (another phenothiazine derivative) and similar agents. Combination of these drugs with narcotics has definite and real advantages such as antishock protection during the induction, maintenance and postoperative periods. There has been a strong tendency to diminish heavy premedication, especially with drugs such as morphine, thus allowing the patient to arrive in the operating room with maximal respiratory and circulatory capacity and function so that the amount of anesthesia with its deleterious effects can be held to a near minimum. Patients emerge rapidly and remain in a quiescent sleeplike state wherein they can be aroused easily and their protective reflexes are still active. However, careless use of tranquilizers may be harmful rather than beneficial, and they must be carefully tailored to the anesthetic technic and to the patient's physiologic requirements.

Hypotension

Hypotensive technics are available but are used only in special situations where bleeding is a major consideration. The wide application this method had in England originally has not been duplicated in this country. Basically the drug used in this country to induce hypotension is Arfonad (thimethaphan camphorsulfonate), a thiophanium derivative whose activity is quickly reversible. The drug acts by reducing peripheral resistance. Hypotensive technics are used primarily in fenestrations, neurosurgical procedures, cardiovascular and vascular surgery, and extensive procedures such as total pelvic eviscerations.

Hypothermia

In selected cases hypothermia is employed as an adjunct to anesthesia. Essentially the technic in this country is one of surface cooling by either immersion or a combination of immersion and cooling-blanket apparatus, or with ice bags alone or in combination. Hypothermia can be divided into three basic types: (1) mild cooling, depressing the temperature only 1 to 2° C., utilized principally for patients who are toxic, stressed or "fevered" and those with rapid metabolism, such as children; (2) intermediate cooling, lowering the

temperature to from 93 to 88° F. (33.5 to 31° C.), used primarily in cardiovascular patients undergoing major vascular reconstructive surgery, in extremely toxic patients with septicemia to lower the metabolic state, and in cases of thoracic and abdominal aneurysm in which there is to be interruption of circulation to a viscus such as the kidney; (3) deep hypothermia, lowering the temperature to around 86° F. (30° C.), employed primarily for surgical procedures with vascular interruption to vital organs such as the brain and heart, in order to protect against anoxic insult.

The problems arising from hypothermic therapy are not yet totally answered. There has been difficulty with blood coagulation, metabolic acidosis, and so on. Therefore, with the possible exception of the mild form of hypothermia, the technic should be reserved for use by those specially trained in its management. "Hypothermic anesthesia" is harmful if one does not utilize an extremely light anesthesia with agents that will prevent reaction to the cold and incipient shivering. The amounts of anesthetic and relaxant drugs must be lowered, and tailored to the extent or degree of hypothermia.

Pediatric Anesthesia

Anesthetic management of infants and children has undergone a marked change. The psychic welfare of the patient has become an important consideration. Children are being brought to the operating room free from fears and tears. This is accomplished with tranquilizing agents and adequate premedication of various types which do not cause excess depression yet sedate the child to a state of near sleep without physiologic harm. Rectal barbiturates are popular for basal anesthesia or light sleep in children, and justifiably so. Morphine is used in ever-decreasing numbers of cases because of its depressive effects on the respiration, cough reflex and autonomic control of blood pressure and because it stimulates the vomiting center. Induction of anesthesia in a child has become almost a game in which the anesthetic state is induced without the child being aware of any irritation, suffocation or other similar undesirable psychic insult. Apparatus now available is designed for the child so that respiration is not labored and easy elimination of carbon dioxide is not impeded. Much of the older apparatus generally available permits accumulation of carbon dioxide and has resistances which result in a greater work load for the child, with physiologic harm.

Increasingly popular are "high flow" technics which allow for effective elimination and nonaccumulation of carbon dioxide and the administration of adequate concentrations of oxygen. There is also a greater awareness of the hazards of hyperthermia or hypothermia because of inability to dissipate heat or too great a dissipation of heat. Use of such items as standard adult drapes in surgery not only prevents proper dissipation of heat but also causes extra work on the part of the small child to carry on respiration. Those who had been using the old "open drop mask" method for years, erroneously assuming it was the safest procedure, received a real shock when scientific measurements demonstrated not only that the oxygen tension under the mask dropped but also that elimination of carbon dioxide was markedly impeded. With the newer technics and proper pediatric apparatus one can now easily assist respiration and assure adequate respiratory function. If the open drop technic is used, oxygen should be insufflated under the mask to assure an adequate supply of oxygen and elimination of carbon dioxide.

Monitors

Instruments of various types have been introduced into clinical anesthesia which have as their purpose to warn, to admonish and to observe patients. They are used to observe the pulse, the electrocardiograph, the electroencephalograph, heart and chest sounds, temperature, carbon dioxide, respiration, etc. They vary from simple single units to complex multiple units primarily of research type. They can be extremely valuable in that by their proper use one can recognize deviations from normal which would ordinarily not be observed. Development of this phase of anesthesia is in its relative infancy, but it must and will progress. It is foolish to use only the

eye, ear and hand; not that these are not the most important technics for evaluation of physical state, but instruments can aid our God-given senses and help us so much more. The scientist can and will produce many monitors that will make anesthesia safer.

Respiratory Assistors

Into the field of anesthesia have come many mechanical aids in addition to the monitors. Most important among them are instruments which assist or control respiration. These units are of many types, but basically they have one common purpose, to assure adequate pulmonary ventilation. Some assist the respiration and permit the patient to cycle the unit. Others work on automatic time, pressure or volume principles. Each unit has advantages and disadvantages. In general the assistors are physiologically better than the controlling devices. The educated hand does a good job, but in many instances with time and fatigue and attention to the many details during anesthesia even the very rare "educated hand" fails to do an adequate job of ventilating the patient. Use of these instruments by anesthetists is justifiably increasing.

Summary

Technics and agents of anesthesia are continuing to change. The changes are brought about by the introduction of newer agents recently synthesized, and also because of better instrumentarium for more dependable control. The great force behind all this is the fact that leaders in the fields of anesthesia and surgery are measuring the effects of anesthesia and surgery by the newer scientific devices. This type of research is rapidly replacing clinical trials and evaluation and causing us to change many traditional concepts. All this is resulting in greater safety for the anesthetized patient.

1958

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 10-13 Municipal Auditorium Cleveland, Ohio

Man, Stress and Motion

Experiments with human volunteers to explore human tolerance to decelerative forces and the application of findings to Air Force problems, vehicular crashes, escape from in-flight disasters of supersonic aircraft, and man's fitness for exploration of space will be discussed. An experiment on a space-equivalent flight by means of a self-maintained capsule which carried a man to more than 100,000 ft. altitude and was aloft for 32 hours and 10 minutes will be presented as evidence of human tolerance to space stress.

JOHN P. STAPP, M.D.

Colonel, M.C., USAF, Chief, Aero Medical Laboratory, Directorate of Laboratories, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio

An Interpretation of the Action of Psychotropic Drugs

BERNARD B. BRODIE, DARWIN J. PROCKOP AND PARKHURST A. SHORE*

National Institutes of Health, Bethesda

BERNARD B. BRODIE

MOST drugs which exert an influence on the peripheral nervous system act at junctions where nerve impulses are transmitted by the neurohormones, acetylcholine or norepinephrine. A drug may affect transmission by a neurohormone if it (1) mimics its action, (2) blocks its action, (3) protects it from destruction, (4) interferes with its liberation, or (5) depletes it from nerve endings.

By analogy it might be expected that drugs influence the central nervous system by modifying chemical transmission at synaptic junctions. Definite proof of this view, however, has not been obtained. The problem is complicated by the relative inaccessibility and diversity of structural elements in the central nervous system. Moreover, until recently, acetylcholine has been the sole neurohormone established for the central nervous system; it is difficult to explain the diverse effects of centrally acting drugs on the basis of a single transmitter substance, especially since some parts of the brain, like the cerebellum, contain little or no acetylcholine.

New avenues for investigating drug action have been opened by the discoveries of serotonin (5-hydroxytryptamine) and norepinephrine in the brain. The extraordinary biologic activity of these amines together with their uneven distribution in the brain makes it reasonable to assume that serotonin and norepinephrine have a specialized function in the areas where they are found. Irrespective of their precise role, it is fruitful to consider that a drug will exert a central action if it mimics or blocks the action of the amines, inhibits their destruction or release, or depletes their stored forms. As discussed later, there is now considerable evidence that a number of centrally acting drugs act in one of these ways.

A function for brain serotonin and norepi-

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TABLE 1

STIMULATION OF DIENCEPHALIC SYSTEMS

(Nomenclature of Hess)

COMPARISON WITH EFFECTS OF RESERPINE AND LSD

	TROPHOTROPIC PREDOMINANCE (OR EFFECTS OF RESERPINE)	ERGOTROPIC PREDOMINANCE (OR EFFECTS OF LSD, MESCALINE, ETC.)
Behavior	Lack of volition and adynamia Decreased reactivity to sensory stimuli Drowsiness, sleep with active closure of eyelids	Increased initiative and emotional responses, increased reactivity to sensory stimuli, arousal and excitement
Skeletal muscle	Decrease in muscle tone and locomotor activity General atony	Increase in muscle tone and locomotor activity Motor excitement
Respiration	Depression	Activation
Autonomic system	Miosis Lowering of blood pressure Bradycardia Relaxation of nictitating membrane Salivation Hypothermia	Mydriasis Elevation of blood pressure Tachycardia Retraction of nictitating membrane Hyperthermia Pilo-erection

nephrine is suggested from the physiologic concepts of Hess.[1] His views are extraordinarily helpful in considering, within a physiologic and biochemical frame of reference, the possible modes of action of a number of centrally acting drugs like reserpine, chlorpromazine, lysergic acid diethylamide (LSD), mescaline and amphetamine. Hess pointed out that the autonomic nervous system is not an isolated entity, since its sympathetic and parasympathetic components must synchronize centrally with the somatic nervous system to maintain body integrity. He studied the nature of the coordination in unanesthetized cats by electrically stimulating various brain areas. From the behavioral patterns Hess postulated that reactions of the mammalian organism to environmental changes are controlled by a subcortical system integrating autonomic, somatic and psychic functions. He further proposed that the subcortical system, like the peripheral autonomic nervous system, consists of two mutually antagonistic divisions (ergotropic and trophotropic).

According to Hess, the trophotropic division integrates parasympathetic with somatomotor activities to produce behavioral patterns that conserve and restore energy. The over-all effects of trophotropic stimulation are sedation, increased parasympathetic activity, decreased skeletal muscle tone and activity, and external stimuli. In contrast, the ergotropic division integrates sympathetic with somatomotor activities to produce patterns of behavior which prepare the body for positive action. The over-all effects of ergotropic stimulation are arousal, increased sympathetic activity, enhanced skeletal muscle tone and activity, and an activated psychic state. Both neuronal divisions are in continuous opposition, the resulting level of activity ranging from trophotropic predominance (sleep or apathy) to ergotropic predominance (excitement or mania).

Recognition of the startling similarity in the effects of certain psychotropic drugs to overactivity of one of the antagonistic subcortical systems has led to a new approach in the study of central integrative mechanisms and also their interaction with drugs. Reserpine sets off a syndrome of physiologic effects similar to those of trophotropic predominance. Contrastingly, the hallucinogenic drugs LSD and mescaline provoke signs like those of ergotropic predominance (table 1).

Considerable data favor the concept that serotonin and norepinephrine may serve as neurohormones of these two neuronal systems. The amines as well as the enzymes involved in their formation have their highest concentrations in the brain stem, especially in the hypo-

thalamus,[2-6] where a major part of somatoautonomic integration occurs. In addition there is an enzyme, monoamine oxidase, which can dispose of the free amines when their functions are completed.[4] Moreover, the presence of the amines in a stored inactive form suggests that something, perhaps a nerve impulse, is required to release the free active form.

There is considerable evidence that norepinephrine and serotonin act centrally in opposite ways. Free norepinephrine in brain elicits effects typical of mescaline and LSD or of overactivity of the ergotropic division. Rothballer[7] reported that norepinephrine administered intravenously to laboratory animals produces excitation and an electroencephalographic arousal pattern. He proposed that a component of the brain stem known as the reticular activating formation contains adrenergic neurons. The activating properties of the reticular formation suggest that it includes the ergotropic component of Hess's unified system. Rather convincing evidence for the view that brain norepinephrine influences an adrenergic system is the demonstration that dihydroxyphenylalanine (dopa), the amino acid precursor of norepinephrine, reproduces signs of ergotropic predominance with remarkable fidelity.[8]

Similar data for serotonin are less clear-cut, but a number of studies have shown that a low concentration of the free amine in brain induces a syndrome typical of reserpine or overactivity of the trophotropic division. Although no single piece of evidence is decisive, the accumulated data suggest that the trophotropic system is a serotonergic system. (1) After giving mice a large dose of serotonin intraperitoneally, small but significant amounts of amine enter the brain and the animals display reserpinelike effects, including sedation and potentiation of hypnotics. The depressant effects of serotonin are blocked by the centrally acting LSD.[9,10] (2) Serotonin induces a general depression of spontaneous activity in rats and partially blocks a conditioned response with doses that do not incapacitate motor function.[11] (3) The administration of low doses of 5-hydroxytryptophan, a serotonin precursor, results in sedation with an electroencephalographic sleep pattern in cats[12] and a hypersensitivity to hypnotics in mice.[13] In higher doses, however, the amino acid elicits signs of excitement.[12] This reversal of effects has been attributed to blockade of the normal action of serotonin by a high concentration of the free amine.[10] (4) Monnier and Gangloff[14] reported a similarity in electroencephalographic sleep patterns elicited by intravenous injections of reserpine and serotonin. (5) Serotonin has been implicated as a neurohumoral agent for the clam heart.[15]

Certain drugs which affect mood and behavior may now be put into two classes: The first group, the *Rauwolfia* alkaloid and the phenothiazine derivatives, elicits sedation and depressed sympathetic activity, skeletal muscle tone, and sensitivity to external stimuli. These effects are similar to those of trophotropic overactivity. The second group, LSD, ibogaine, mescaline and ephedrine, for example, elicits opposite or ergotropic signs. These drugs produce excitement and increased sympathetic activity, sensitivity to external stimuli, and skeletal muscle tone.

Drugs That Produce the Trophotropic Syndrome

The concept of opposing subcortical divisions makes it possible to describe the action of certain central tranquilizing drugs in two ways: (1) by stimulation of the trophotropic division or (2) by paralysis of the opposing ergotropic division. We can now see how chlorpromazine and reserpine produce similar central effects even though they are known to act by different mechanisms.[10] The difference in the modes of action of the two tranquilizing drugs is best explained on the assumption that they act on physiologically antagonistic divisions, reserpine by stimulating the trophotropic system, and chlorpromazine by blocking the ergotropic system.

Reserpine does not exert its effects per se but appears to act indirectly, since its pharmacologic action persists long after the drug has disappeared from the body. The alkaloid has the singular property of impairing the capacity of brain cells to store serotonin.[9] It is pertinent that all drugs shown to release sero-

tonin also elicit reserpinelike effects.[9] With impairment of the storage sites, free amine now leaves the brain cells in a continuous stream. The action of the drug has been attributed to the highly active free serotonin which stimulates the receptor sites of the trophotropic division until the serotonin storage mechanism regains its function.[10] Stimulation of the trophotropic system should be manifested by increased parasympathetic tone; accordingly, reserpine elicits pupillary constriction by central parasympathetic stimulation. Other parasympathetic effects of reserpine include lacrimation, nasal secretion and an enhancement of the light reflex.

Recent studies have demonstrated that reserpine also interferes with the storage of norepinephrine in the brain,[16,17] and it might be argued that this amine is released continuously to subcortical synapses. However, the effect on brain serotonin appears to be the important factor associated with reserpine action. Thus, in studies relating the sedative effect of reserpinelike compounds to the release of brain amines, a close relationship between the sedative potency of reserpinelike drugs and the extent of serotonin release is manifested. All of the compounds, however, do not exhibit a similar relationship between norepinephrine release and sedation. An additional indication that reserpine action is mediated through free serotonin is the exceedingly rapid formation of serotonin in brain—about 50 times more rapid than that of norepinephrine.[18]

Reserpine also depletes norepinephrine stores at peripheral nerve endings.[17,19] This depletion of norepinephrine is an extremely important factor in the peripheral action of reserpine since sympathetic nerve impulses cannot influence effector organs when no neurohormone is available at nerve endings. Thus, reserpine exerts two distinct and separate actions on the autonomic nervous system, a peripheral action which lowers sympathetic activity due to its effect on peripheral norepinephrine and a central action which increases parasympathetic activity through its effect on brain serotonin.

The general opinion that the sedative and hypotensive actions of reserpine have a common central mechanism must now be revised. In fact, reserpine depletes peripheral norepinephrine stores and lowers blood pressure at doses which have only a minor effect on the brain amines and elicit little sedation. These results indicate that a major difficulty in managing hypertensive patients by means of reserpine is maintaining a dosage schedule that selectively releases the peripheral norepinephrine without releasing enough of the brain amines to elicit depression. Of considerable interest, therefore, is the new reserpine analogue Su 3118 (figure 1), which appears to

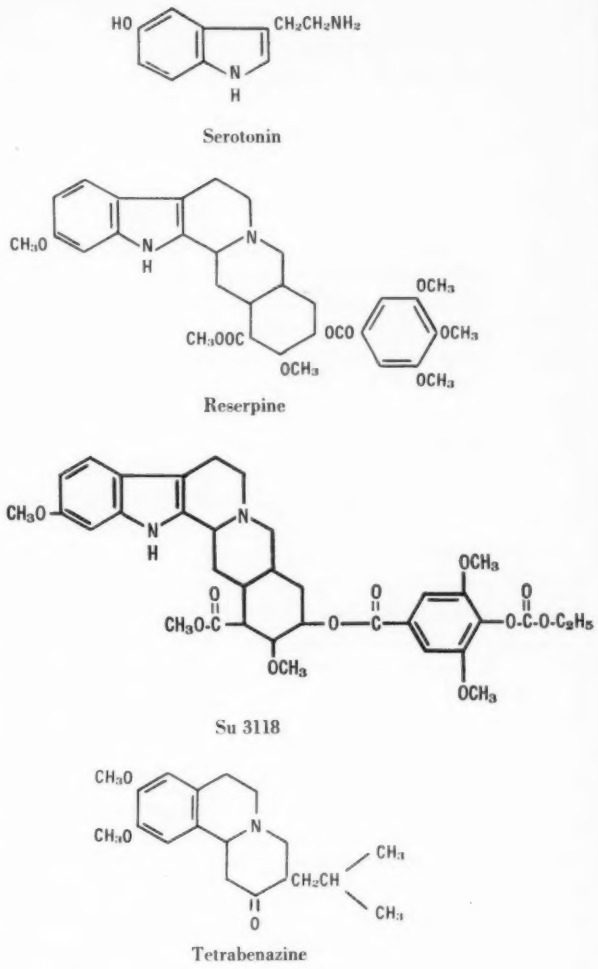
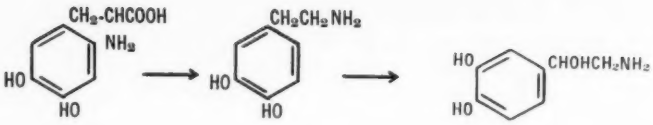


FIGURE 1.



Dopa Dopamine Norepinephrine

FIGURE 2.

have a predominantly peripheral effect.[20] It releases peripheral norepinephrine but appears to have a very small influence on the brain amines. Consequently, animals can be maintained on doses of the drug which elicit a drop in blood pressure and pulse rate without producing overt sedation.

Reserpine is usually regarded as an "antimetabolite" of serotonin since both substances possess the indole structure. Of great interest, therefore, is the report that tetrabenazine, a nonindole, releases brain serotonin and norepinephrine and elicits reserpinelike central effects.[21] Since the drug acts rapidly and has a short duration of action, it may have some advantages over reserpine in treatment of mental illness. We have found that tetrabenazine does not have the dual action of reserpine; it releases serotonin and norepinephrine in brain but does not appreciably affect norepinephrine at peripheral nerve endings. Consequently, this drug should be more useful as a tranquilizing agent than in the treatment of hypertension.

Chlorpromazine, in contrast to reserpine, does not release serotonin or norepinephrine. The drug appears to act by blockade of the ergotropic system through interfering with the action of brain norepinephrine. Presumptive evidence that it acts this way may be shown by its influence on the central effects of dihydroxyphenylalanine (dopa), the previously mentioned norepinephrine precursor, which enters brain and yields dopamine and norepinephrine (figure 2). The stimulatory and increased sympathetic effects induced by dopa are dramatically blocked by chlorpromazine but not by reserpine.

Drug-induced depression of the ergotropic system should be reflected by decreased sympathetic discharge from the central nervous system. Accordingly, chlorpromazine produces pupillary constriction and lowers blood pressure by suppressing sympathetic activity. It does not elicit parasympathetic effects such as lacrimation, nasal secretion and enhancement of light reflex.

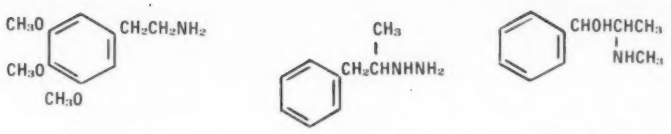
In contrast to reserpine, chlorpromazine has little direct peripheral action. In fact, virtually all the autonomic and somatic effects of chlorpromazine are elicited by injection of the drug into the cerebral ventricles in amounts too small to have any effect after intravenous administration.[22]

A number of other adrenergic blocking agents also have a central chlorpromazinelike action, but to a lesser degree. For example, the dihydroergot alkaloids have a mixed effect. They exert a peripheral adrenergic blockade by interfering with norepinephrine action at nerve endings, but, in addition, cause sedation, depress skeletal muscle tone, and lower sympathetic activity by suppressing the ergotropic system in the brain. Chlorpromazine and other phenothiazines are characterized, however, by their predominant effect on the central nervous system. Perhaps a new term, central adrenergic blocking agent, should be used in order to describe the central actions of chlorpromazine.

Drugs That Produce the Ergotropic Syndrome

Certain central stimulants may also be described according to their influence on the antagonistic neuronal divisions in the subcortex. A drug may produce the ergotropic syndrome, directly by stimulating the ergotropic division, or indirectly by unmasking this system through paralysis of the opposing trophotropic division.

Mescaline and a number of other compounds including amphetamine, ephedrine and desoxyephedrine are phenylethylamine ana-



Mescaline Amphetamine Ephedrine

FIGURE 3.

logues of norepinephrine (figure 3). They differ from norepinephrine in an important respect: Being lipid-soluble they readily penetrate the brain and exert a pronounced central action. These drugs may be considered to imitate the action of norepinephrine at ergotropic receptor sites, thereby inducing arousal, increased central sympathetic outflow, increased psychomotor activity and enhanced sensitivity to external stimuli. Indeed, they elicit signs in animals that closely resemble those induced by dopa, the norepinephrine precursor. Formerly, the central and peripheral effects of amphetamine and ephedrine were attributed to two separate and distinct actions. Excitation and increased psychomotor activity were a central or analeptic action; while the increased sympathetic reactivity was an influence at peripheral sympathetic sites. Though these compounds exert some influence by a direct peripheral action, their adrenergic effects result largely from increased sympathetic outflow from the central nervous system. Here, too, a new term, central adrenergic agent, might be used.

LSD, the most potent of the ergotropic drugs, is both an indole and a phenylethylamine. Conceivably, therefore, it might depress the trophotropic division by competing for serotonin at its active sites or stimulate the opposing system by mimicking the action of norepinephrine. It is particularly noteworthy that not only LSD and mescaline but ergotropic agents in general, including amphetamine and ephedrine, when given in sufficiently large doses, induce aberrant behavior and illusions in man. This suggests that the reversible psychoses produced by these agents are an inevitable response of a highly tuned ergotropic system.

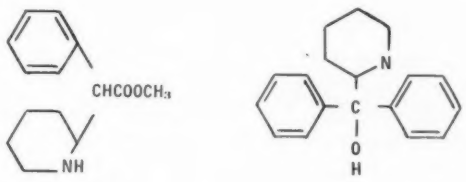
Two centrally acting phenylethylamines, methylphenidylacetate (RITALIN®) and pipradrol (MERATRAN®) (figure 4), exert only a minor direct action on the peripheral autonomic system and are used in treating the depressed patient.

Drugs That Inhibit Destruction of Norepinephrine and Serotonin

Iproniazid (MARSILID®), a hydrazine derivative of isonicotinic acid, was discarded for the treatment of tuberculosis because it induced effects of a central stimulatory nature. Loomer, Saunders and Kline[23] at Rockland State Hospital in New York took advantage of the side effects and found the drug to be effective in treating depressed mental patients.

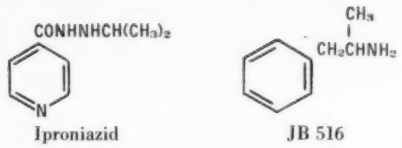
Iproniazid appears to act by inhibiting monoamine oxidase,[24] the enzyme mainly responsible for the physiologic inactivation of brain norepinephrine and serotonin. When iproniazid is given to animals in small daily doses the levels of the brain amines progressively rise until they are two or three times their normal values, and a variable degree of psychomotor excitation appears.[25] Incomplete studies suggest that the increase in brain norepinephrine may be responsible for the stimulatory effects of the drug.

Other monoamine oxidase inhibitors also raise the level of the brain amines and elicit central excitation. In particular, JB 516, a hydrazine analogue of amphetamine, acts more



Ritalin Meratran

FIGURE 4.



Iproniazid JB 516

FIGURE 5.

rapidly and is far more potent than iproniazid. When given to animals in very small doses it also raises the brain levels of the amines and induces pharmacologic effects similar to those seen after iproniazid.[25] (Figure 5.)

Numerous hydrazine monoamine oxidase inhibitors, currently under investigation, inhibit the enzyme irreversibly. Consequently, their effects are cumulative when daily doses are given. As a result they have a slow onset of action that persists long after drug therapy is stopped. Attempts are now being made to develop a reversibly acting monoamine oxidase inhibitor whose action occurs rapidly and is dissipated as soon as the compound disappears from the body.

As yet, the over-all pharmacologic effects of monoamine oxidase inhibitors do not fit a clear pattern. Despite a central excitatory action, they lower blood pressure;[26] they may have some use in the treatment of hypertension. They are also reported to be of value in the control of angina,[27] possibly due to the sparing of norepinephrine normally released from sympathetic nerve endings in the heart.

An interesting new development in our laboratory concerns the effects of monoamine oxidase inhibitors on experimental convulsions. Earlier studies by Chen, Ensor and Bohner[28] showed that reserpine lowers the threshold for electroshock and METRAZOL® convulsions in laboratory animals. Since monoamine oxidase inhibitors increase the brain levels of the same amines which are depleted by reserpine, we decided to test these drugs against seizures caused by supramaximal electroshock in rats.

Iproniazid, JB 516 and other inhibitors were found to suppress the tonic extensor phase of electroshock seizures. The drugs do not act immediately, and exert their maximal effects when the brain levels of the amines are increased twofold to threefold. There is a close relationship between the duration of the elevation in brain amines and the duration of the anticonvulsant effect. It is noteworthy that diphenylhydantoin (DILANTIN®) exerts a protective action against electroshock in doses which do not elevate the levels of brain amines.

The converse effects of reserpine and monoamine oxidase inhibitors on electroshock convulsions suggest that their actions are not due to the drugs per se but are related to the opposite changes in brain amines. Support for this view is obtained from experiments in which both reserpine and iproniazid are given to the same animal and different effects are obtained, depending on which drug is administered first.

When reserpine is given two hours *before* iproniazid the stores of brain amines are depleted. As a result electroshock seizures are enhanced. On the other hand, when reserpine is given two hours *after* iproniazid the brain amines are not lowered, since the released substances are protected from the action of monoamine oxidase. As a consequence electroshock seizures are blocked. Not only do these observations indicate that the influence of reserpine and monoamine oxidase inhibitors are indirect but they suggest that the monoamine oxidase inhibitors protect against electroshock convulsions through the accumulation of free amines in brain. The data available at this time do not permit a positive conclusion as to whether free serotonin or norepinephrine or some other amine is involved in the anticonvulsant action produced by the monoamine oxidase inhibitors.

Further studies have demonstrated that monoamine oxidase inhibitors also protect against the tonic extension phase of convulsions evoked by intravenously administered pentylenetetrazol (Metrazol) in mice.

It is still too early to predict whether monoamine oxidase inhibitors will be of value in epilepsy or will add to our understanding of the disease, but these possibilities are under investigation.

Comment

Behavioral mechanisms which can function without conscious control are regulated by

subcortical systems that synchronize autonomic, skeletal muscle and psychic functions. The action of a number of behavior-affecting drugs may be explained in physiologic terms by Hess's view that the activity of these functions is coordinated by two antagonistic divisions: ergotropic and trophotropic. As a working hypothesis the central actions of these drugs are ascribed to their interaction with adrenergic or serotonergic receptor sites.

On this basis, certain tranquilizing agents may influence behavior by shifting the balance of the opposing systems toward trophotropic predominance: reserpine by stimulating the trophotropic system, chlorpromazine and its analogues by suppressing the opposing ergotropic division. The resulting level of activity results in sedation, decreased response to sensory impressions, a decline in skeletal muscle tone and active movement, and a decrease in sympathetic activity. In contrast, certain central stimulants may affect behavior by shifting the balance of opposing subcortical activities toward ergotropic predominance: mescaline, desoxyephedrine and Ritalin by activating the ergotropic division, LSD possibly by suppressing the opposing trophotropic division. In addition, the monoamine oxidase inhibitors may produce ergotropic predominance by causing an increase in the level of norepinephrine in the brain.

The question arises as to what psychotropic drugs do in patients with mental disorders. The results of the clinical use of reserpine in mental disease indicate that reserpine and chlorpromazine are most effective in patients with mental disorders manifested by hyperactivity and exaggerated emotional responses. These patients may be said to have highly tuned ergotropic systems and often require large doses of a tranquilizing agent to swing the balance in the opposite direction. It is logical to presume that reserpine or chlorpromazine does not alter the basic defect in mental illness but provides symptomatic relief by decreasing ergotropic overactivity. As a result the drugs blunt initiative by decreasing psychomotor activity and lowering the responsiveness to endogenous and exogenous stimuli. Mood-elevating agents such as amphetamine, Ritalin and the monoamine oxidase inhibitors have been found to be useful in the treatment of depressed patients by causing the balance to swing in the direction of ergotropic activity.

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1958

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 10-13 Municipal Auditorium Cleveland, Ohio

Behavior Problems of Children

A discussion of some of the urges in children's actions and suggestions for directing these urges toward developing good social adjustment will be included in this address. The prevention of pressures, the desirability of consistency in management, and the results of good morale and family love will be considered.

JOHN G. YOUNG, M.D.

Clinical Professor of Pediatrics, University of Texas Southwestern Medical School, Dallas

Ethics and New Drugs

M. J. SCHIFFRIN*

University of Illinois College of Medicine, Chicago

M. J. SCHIFFRIN

MEDICAL practitioners, scientists and manufacturers have as a common goal the development and use of safer and more effective means of treating and preventing human suffering and disease. There are enormous difficulties in attaining this desirable end. These consist, in part, of technical, scientific, medical and legal problems in each step from the original concept of a drug to its acceptance in good medical practice. Above these problems, and yet affecting all of them, is the attitude of those who labor in every phase of this development. Such men of good will, who work toward bettering the lot of mankind, have an approach and attitude toward their tasks that reflect their personal and professional ethics.

A very large measure of the responsibility for medical progress is in the hands of the general practitioner. He must decide why to act, what to use, how to treat, and when to take a course of action, whenever he sees a patient. He knows that no one can be certain of success all the time. Medicine is practiced on the basis of probabilities, and he will therefore have to choose that technic which in his opinion offers the best chance of success in *each particular patient and circumstance*. His problem regarding new drugs can be stated simply: "Will this be better for the patient?" The answer to this is in many ways the same as that for the medical scientist and manufacturer in that it can be found by using in an ethical manner the best knowledge and skill available.

Some of the ethical questions relating to new and experimental drugs that are to be discussed are as follows: What is a new drug? Who is an investigator? What is the nature of a human volunteer? When is a patient a proper research subject? What are some of the ethical responsibilities of the manufacturer? These questions by no means cover all the areas pertinent to the subject, but represent some of the more common problems.

What Is a New Drug?

A "new" drug as described herein is any drug recently approved by the Food and Drug Administration, or any drug with which the

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physician is not familiar. An "experimental" drug is one that has not been submitted to the Food and Drug Administration, and whose place in therapy is not determined.

I have analyzed a recent issue of one of our most respected national medical journals. Twenty per cent of its pages are devoted to original reports of medical studies. No less than 36 per cent of its pages are covered with advertisements for drugs. Eighteen full pages are given to advertisements for "new" drugs. Does this mean that there are 18 genuinely new drugs? I estimate that there are already about 5000 pharmaceutical preparations, most of which have individual trade names that bear little resemblance to the active ingredients. The number is increased by the multiplicity of dosage sizes, tablets, capsules, syrups, elixirs, ointments, ampules, vials, suppositories, lotions, powders, etc. *ad nauseam*. How does one decide what is really new or significant? Can a physician accept the criteria of the law, the manufacturer, the advertising executive, the salesman, or even the published article by a recognized medical "authority"? Or should each physician determine his own criteria of a new drug?

Federal law, operating through the Food and Drug Administration (FDA), has jurisdiction over drugs transported across a state line. The FDA therefore can act only on those items related to *interstate* shipments. A manufacturer who does not make a shipment outside the state is usually free of FDA supervision, and he operates within the law if he meets his local and state requirements. These local requirements vary greatly. In general, the FDA considers as an experimental drug a new chemical, any new vehicle or dosage form, a new combination of drugs, or a new indication for an older drug. Physicians must recognize the fact that the FDA is in most instances apparently more concerned with the safety of a drug than with its effectiveness.

Every manufacturer who works with an experimental drug must keep a special register showing all shipments of the material. Before the manufacturer can send the drug to a clinician, the investigator must sign a new-drug release form. This is a statement of the investigator's qualifications and facilities and the manner in which he will use the drug. The release form also carries a statement that the investigator is familiar with the appropriate sections of the law relating to new drugs. The manufacturer is legally permitted to make interstate shipments of the material after he has the investigator's signed release form on file. If the manufacturer wants to market the drug and place it in interstate commerce, he must file a new-drug application with the FDA. This application contains all the pertinent laboratory and clinical data. The FDA reviews the evidence and, if it is satisfactory, permits the manufacturer to make the drug available for sale. It is at this point that most physicians first become aware of the new drug through the media of advertising and salesmen.

In brief summary, then, the FDA definition of a new drug is broad in one sense, but one has the impression that it is more concerned with safety than with effectiveness; also, the definition applies only to drugs in interstate shipment.

The manufacturer and his advertising agency may have quite another definition of a new drug. They include all that which the FDA classifies as new and add to it items not covered by the law. For example, a container of a new shape, composition or color would not interest the FDA yet might well be the basis for an advertising campaign featuring the word "new." It is an idiosyncrasy of our American civilization that anything new must be better, and it necessarily follows that the newest is the best. Anyone who doubts this has only to look at our automobile industry. Physicians are people, and they are as susceptible as the rest to the lure of change and newness. Advertising new drugs to the medical profession is no different from any other type of advertising.

There is some truth to the old definition of an authority as being any so-and-so from out of town. Is it proper for the physician to take at face value the report on a new drug made by an "authority" in a reputable medical journal? Let me point out one pitfall. Statistics are valuable tools in medical investigations, and the science of biostatistics has become in-

creasingly important and helpful. Yet how many physicians know the meaning of "student 't' test, multiple covariant analysis, 'P' value, and Chi square"? I have asked this question of good third-year residents and learned to my dismay that many were not aware of the meaning or significance of these terms. What, then, can we expect of the general practitioner who graduated 20 years ago?

When we read the report by the "authority," we usually find expressions of statistical values. These statistical data become very impressive because in general we set a high value on what we do not understand. Therefore, if the conclusions in the report seem a little farfetched to us we say, "and yet it must be so because the statistics prove it." The truth is that statistics *under certain conditions* give us an expression of *probability*. We all understand what is meant by odds of better than 20 to 1, and this is what is expressed, in the main, by the exotic term "$P < 0.05$." Most important of all is the maxim that the statistical probability is no more significant than the validity of the data from which it is derived. If the experiment is poorly designed, controlled or measured, then no amount of statistical analysis will give the conclusions any real validity. It remains true, however, that authoritative documented evidence in reputable medical journals is the best outside reference for the physician in search of knowledge about a new drug. The larger the number of such authoritative references, and the more closely their conclusions correspond, the greater is the reliability that can be placed on their report of the characteristics of the new drug.

In the final analysis, should the physician unreservedly accept anyone else's definition or description of a new drug? A physician might choose to classify as a new drug any therapeutic agent with which he is not completely familiar. Accordingly, unless he at least knows the clinical pharmacology and toxicology of the drug, and has had personal experience with its use, he might consider it a new drug. The practitioner has a most difficult problem in trying to keep up with advances in therapy. He has to put considerable time and effort into meeting this challenge. It would therefore appear that if the physician took a most critical and demanding view of new drugs, he and his patients would profit, since he would be engaged with only those drugs representing significant advances in therapy.

Who Is an Investigator?

Experimentation on human beings and the role of the investigator have been the subjects of many publications and reports.[1-10] In the decision of the Nuremberg medical trials, the statement is made, "The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment."[11] Who is a scientifically qualified person? Does the M.D. or Ph.D. degree confer sufficient qualification? What of the possessor of the master's or bachelor's degree in science? "The highest degree of skill and care should be required" describes the court's *opinion*, but who has the responsibility for actually measuring and determining the degree of skill and care required for each proposed study on human beings? This must rest on the responsible investigator who makes the decision on the basis of his experience, knowledge, ethics and the dictates of his own conscience. The practitioner with an M.D. degree may be licensed by law to practice medicine, but does this, ethically, qualify him to study all *experimental* drugs on volunteers or patients? The biologist who has earned the Ph.D. degree is usually considered to have the basic skills in his specialty, but under what circumstances, if any, can he ethically engage in human experimentation? Is it possible for a man to have both the M.D. and Ph.D. degrees, plus certification in his medical specialty, and still not be qualified ethically as a senior investigator in human experimentation?

These questions are not easy to answer. Consider the academic and professional qualifications of those who engaged in the Nazi medical crimes. In spite of their technical competence, did they have the moral and ethical qualifications? In a discussion of the background of the atrocities committed by the Nazis, Ivy[9] made the very significant state-

ment, "One (of the factors) was a debased regard of the duty of a physician toward poor and underprivileged patients." We must not allow ourselves to be self-righteous or smug. Misadventures and even deaths have been known to occur during human experimentation in this country.

In summary of this section, it appears that there are moral and ethical qualifications for those who engage in experimentation on human beings. There is a need for special training in clinical research, as Stetten[7] and Kohlstaedt[8] have so ably indicated. Related to this is Vannevar Bush's[12] plea for a better collaboration between the physician and the scientist. The truly qualified medical investigator will seek out all the help and collaboration he can obtain from other scientists. In Bush's words, "For, if they grasp one another's mores and traditions, methods of thought, deep convictions, and motivations, there will be no further need to stimulate collaboration of the highest sort. It will occur automatically. And from it will result a surge forward on that complex task of understanding life, where the skill of all professional groups will be strained to the utmost, a new accomplishment which will place a firmer foundation under the keystone of that honorable profession to which medical men belong, ministry to the people."

Who Is a Normal Human Volunteer?

Referring again to the Nuremberg medical trials decision we find, "The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision."[11]

The first parts of these statements are generally understood and accepted; however, the qualification that the subject should have "sufficient knowledge and comprehension" is less well recognized. A responsible investigator will, of course, inform any prospective volunteer of the nature of the study, its purpose and the hazards that might be expected, but of what avail is this if the subject does not have the intellectual capacity, training and experience to comprehend fully the risks and the unknown elements in the experiment? For example, medical students are used as volunteers so often that the term "normal human volunteer" has almost become synonymous with "medical student." But do medical students always have the knowledge and judgment to make an intelligent decision as to whether or not they choose to be a volunteer? When you were a second-year medical student, were you qualified, in the light of your present experience, to decide to volunteer for an experiment involving a new barbiturate, a new anticoagulant, or a new spasmolytic? What of experiments which would require an arterial puncture, liver biopsy or cardiac catheterization? It is apparent that the *quality* of the consent is an important consideration, and that the determination of this quality is a moral and ethical duty that the investigator must recognize and accept.

It remains that in the final analysis the responsible investigator is best suited to make such decisions if he has first performed the experiment on himself so that he can, by personal experience, make a better estimate of the risks involved. This principle of self-experimentation before asking for volunteers is a characteristic of every great investigator I have known. For example, I recall a preparation that was alleged to have curarelike properties when taken in the form of sublingual tablets. One investigator took the usual dose without any obvious effect, and he therefore continued to take the drug until he had consumed 10 times the recommended dose within 30 minutes. He did this before he even considered the possibility of asking for volunteers for the study.

Self-experimentation has at least one other advantage in that it enables the investigator to check his procedure for errors without subjecting others to unnecessary risks. No matter

how carefully the experiment may be designed, human errors can appear. Sometimes these are so obvious that nobody ever thinks of them! For example, I still have vivid memories of what happened 20 years ago when I overlooked the importance of temperature and instilled 200 ml. of a *cold* solution into my jejunum via a Miller-Abbott tube!

In addition to the requirements of a qualified consent, there are other limitations of the right of a person to volunteer for experimentation on himself.[13] These limitations are primarily related to the question, "To what extent can a person consent to serious injury on himself?" For example, a person cannot legally consent to his own death. Also, one cannot consent to an injury amounting to a maim. This may be so for the normal human, but what of the first patients with prostatic carcinoma who consented to orchiectomy?

The volunteer subject in research is not necessarily a "normal" person. Lasagna and Von Felsinger[14] studied 56 apparently normal young men, 21 to 28 years of age, most of whom were college students. These men were volunteer subjects for pharmacologic studies. Appropriate tests revealed that 25 of the 56 men had severe psychologic maladjustments. Thus, the *appearance* of normality was not a valid criterion of the characteristics of this group of volunteers. This means that the psychologic quality of volunteers cannot be taken for granted. This becomes particularly important in the testing of drugs that alter subjective symptoms. In many instances, it is desirable to have as normal a test group as can be obtained. There are, however, some circumstances in which the trials may be more revealing if they are made on an abnormal group of subjects.

Critical and thorough studies of the effects of experimental drugs on animals are the minimal prerequisites to the use of such agents in normal human volunteers and patients. When such studies are properly carried out, they make the initial trials in man that much safer. They also may provide data to aid the investigator in assessing the risks of the study in man. There are at least two important exceptions to the degree of benefit that may be obtained from studies in animals. First, there are situations where the exact counterpart of human disease is not available in animals. In such instances the ethical considerations relating to the use of human volunteers are magnified. Second, even if an experimental drug has a clean bill of health from the laboratory, its use in man may reveal unsuspected toxicity. The use of normal human volunteers for the study of such an apparently safe drug always carries some risk. For example, I recall one drug which was relatively safe in both acute and chronic tests in the laboratory, and seemed to have many advantages over the older preparations which produced the same general pharmacologic effect. When used in man, however, this drug frequently produced alopecia and an intractable diarrhea. Should we not consider every study on normal human volunteers with an experimental drug as a step into the unknown, with all its uncharted dangers?

When Is the Patient a Proper Research Subject?

One of the fundamental difficulties facing the physician in the matter of research on patients has been described as follows by Kidd:[15] "It is the business of the doctor to do his best for his patient. Research on the patient for purposes other than his welfare has no place; yet, if the doctor is not also a research man, he is not the best kind of doctor, and if the research specialist is not interested in the welfare of the patient entrusted to him, he is not the best researcher." Experimentation in its broadest sense must be practiced by all physicians engaged in the art and science of medicine. Frequently the determination of the proper diagnosis can be made only through experimentation. When a patient is given digitalis for the first time, is this not a form of experiment? The nature of the patient, his disease, and the experimental procedure or new drug all play a part in determining if the patient is a proper research subject.

The nature of the patient is a legal and ethical factor in many instances. For example, are the feebleminded, the insane, children, and unconscious patients proper research subjects? If so, under what conditions? Should wealth

and social position, or lack thereof, influence the selection for experimentation?

The disease being treated has a large influence on the selection of the patient as a research subject. The patient who has subjective *symptoms* which in themselves do not threaten life requires very special care. For example, let us consider tranquilizers, which are used as a chemical shield between the individual and his environment. Should an experimental drug in this class carry with its use potential dangers greater than those of the patient's original complaint? For example, should there be a possibility of habituation or addiction? Should not the safety characteristics of all drugs intended for symptomatic treatment of a disease be of the highest order? The assay of drugs which alter subjective responses is one of the most difficult in the entire field of clinical research. We are indebted to Beecher[15-17] and Moyer,[18] among others, for helping to plot a course in this exceedingly difficult area.

Diseases whose natural courses offer objective means of measurement constitute another category. In this group, I include those infectious diseases which, if untreated, would cause a considerable morbidity or mortality. Let us suppose that the organism that causes the disease is known and can be studied in the laboratory, and that there are measurable clinical criteria of the course of the disease. Some of the questions relating to the use of experimental drugs in the treatment of such a disease are as follows: Is there any known curative drug? What is the evidence that the new preparation may be safer and more effective in man? Is the disease more dangerous than the drug's toxicity? Would the use of the drug be a calculated risk that could be justified ethically? Is the use of the drug intended for the patient's benefit? Would you use it on members of your own family if they had the same disease? It is pertinent to note here that Salk's own children were among the first to be given his vaccine when it was still an experimental material.

The problem of the "hopelessly incurable" is a special situation. May such patients, with their consent, be used as research subjects for drugs or procedures that cannot benefit them but may help humanity? And what of heroic experimental surgical technics, or untried and dangerous drugs that might be to their benefit? I suggest that every physician could profit by reading Guttentag's[3] excellent article on the physician's point of view of experimentation on human beings. In particular, I follow his discussion of the hopelessly incurable. Are we not all hopelessly incurable? Is not death the inevitable consequence of life? The very word "mortal" means subject to death. In some rare instances is the use of "hopelessly incurable" a means by which an investigator tries to justify relatively dangerous experiments? Is this a matter of self-deception? What of the patient who offers himself in a spirit of self-sacrifice? How does the ethical investigator respond to this? What happens to the patient-physician relationship under these circumstances? I can think of no better way to summarize than by quoting Guttentag: "Experimentation on the so-called hopelessly sick requires, therefore, a tremendous amount of self-criticism, self-discipline, and understanding of life's essential attributes, lest it be perverted to unconscious barbarity."

The characteristics of the drug or procedure to be used also influence the problem of the patient as a research subject. There are significant differences between an *experiment* involving the first administration of a drug to man, a *therapeutic trial* which follows the initial experiments on human beings, and a *clinical study* intended to expand our knowledge of an agent that has undergone therapeutic trials. Sometimes the study can be a matter of dosage of an established drug. For example, if an investigator wants to study the effects of DEMEROL® on patients in the recovery room he has to make certain decisions regarding the dosage and route of administration. Let us assume that for technical reasons he decides to give the drug intravenously. Is every postoperative patient a suitable subject? Should he use only those whose pain requires a narcotic? Would it be proper and ethical to use a dose of 50 mg. of Demerol? What about 100 mg.? And 200 mg.? Which patients would be proper subjects at each dose level?

Another example might be a new antimetabolite that is not chemically related to any agent accepted for use in the chemotherapy of malignancy. Animal experiments have shown that it is very toxic but effective against many types of experimental malignancy. (There are many drugs of this nature which have proved ineffective in human therapy.) The investigators agree that this drug is worthy of trial in man. Should it be used on the patient with a solitary, operable tumor? Is chronic granulocytic leukemia a proper indication? What of acute leukemia? Should it first be tried on the case of metastatic prostatic carcinoma? Or should its first use be reserved for the patient who is suffering from an inoperable, far-advanced malignancy? If the drug is used only on the "hopeless" case, may we miss beneficial effects that might be seen if the drug were used in the earlier stages of the disease?

What Are the Ethical Responsibilities of the Manufacturer?

It has been estimated[19] that the pharmaceutical industry in the United States spent 127 million dollars for research in 1957. This represents about 7.5 per cent of sales. This is an impressive sum to spend on research, but there are ethical questions that go beyond the responsibility of the manufacturer to support research. At the very first, it would be interesting to know how much of this money supported the search for genuinely new agents, and how much was spent for "research" on mixtures of known drugs, new vehicles and minor modifications. This is no attempt to belittle the contributions of the pharmaceutical industry to medicine, or to discount the recognition and emphasis that this industry places on research. Indeed, I believe that the drug manufacturers place a greater percentage of their sales dollars into research than does any other industry. The primary business of the pharmaceutical industry is to produce drugs for a profit. They know this can best be done through research. Theirs is an honorable business, especially when the patient and the physician profit from the firm's activities. The dollar profit motive is under attack from many quarters but there is no doubt that this motivation has resulted in more competition, and that this in turn has given the physician and patient better and cheaper drugs, and a greater selection of drugs from which to choose.

One of the best friends the pharmaceutical industry has is the physician-investigator who gives his candid criticism of the operations of the industry. As an example, Dowling,[20] in an excellent report, has made three suggestions: "(1) that they emphasize basic research and the discovery of new drugs and avoid minor variations of existing drugs; (2) that they weigh the proposals of their sales departments in the light of advice from their scientific staffs and from competent impartial clinical investigators, and (3) that they revise their advertising methods." Some of the questions arising from these suggestions follow: How much of a research budget should go into the search for new drugs and how much for minor variations for the purpose of having something "new"? How great an influence shall market research exert? Would market research reports have led to the medical research that brought forth the first sulfonamide, the first antihistamine, penicillin or the tranquilizers? Should advertisements appear before any clinical report is made in a reputable medical journal? For example, I have before me two separate full-page advertisements from a reputable journal. One page has 16 good references to the drug being advertised. The second page, promoting another new drug, has only three references; two are "personal communications" and the third is a manuscript "in press." In the same vein, the ethical manufacturer does not use half a dozen preliminary reports as the basis for an advertising campaign featuring the "proved" merits of a new drug. Advertising by innuendo, implication, inference, suggestion and half-truths is not practiced by the ethical manufacturer.

An extension of advertising in medical journals is found in the lay press, radio and television. Public interest in medicine is such that it is relatively easy to use these media to proclaim the alleged virtues of a new drug. This not only may raise false hopes and fears, but it also presents the practitioner with the un-

necessary and difficult problem of handling the patient who rushes in demanding treatment with this latest wonder drug.

Should experimental drugs be sent out to any physician who will accept them or should their original use be restricted to the best-qualified investigators? Should the manufacturer accept as his standards for laboratory and clinical research the *minimum* that will meet the requirements of the Food and Drug Administration?

The physician is the object of advertisements by the pharmaceutical industry because he is the consumer. Yet does he have a real appreciation of the important role he plays in influencing the activities of this industry? A letter from a practitioner to the president of a firm will have more effect than he, the practitioner, realizes. If the physician uses a combination of drug X plus drug Y put out by one company, market research will report this, and, within a year, a dozen other companies will try to sell competitive combinations. If physicians do not use the original combination, it will soon disappear from the market and will not spawn any imitations. The physician who is an editor has special responsibilities for medical advertisements. This problem has been so ably discussed by Garland[21] that his article is recommended to all physicians.

Summary

I agree with Batterman[22] that "the future of a drug depends on what it can do in the hands of the general practitioner and not what it should do on the basis of experiments." In spite of all the best efforts of investigators, manufacturers and federal agencies, the true worth and safety of a new drug may not be established until it has been subjected to as much as five years of use—and abuse. An editorial in the *Journal of the American Medical Association*[23] entitled "The use of new drugs" concludes with these words:

"Physicians today have remarkable tools with which to practice medicine. But, as is true of all tools, improper use is attendant with danger. If there is an unusual risk associated with the use of a drug, but the physician is convinced the drug is necessary for, or at least best suited to, a patient, he should accept the risk as a challenge by which he cautiously approaches his clinical problem. To indict a drug or all drug therapy because occasional reactions are seen is unfair to patients who might benefit therefrom. However, he cannot afford, for his patient's welfare or his own reputation, to use a drug with which he is not familiar or which he believes is too dangerous for his practice. In the final analysis, his decision must rest on his knowledge and experience and on sound judgment."

Research in animals, experiments on human beings, therapeutic trials, and clinical studies are interdependent and necessary steps in the progress toward the development of better agents for the prevention and treatment of disease. Medical scientists who have the privilege of carrying out this program must recognize and accept the ethical as well as the scientific responsibilities related to each step. The general practitioner faces what may well be the most difficult task of all—that of separating the useful, the harmful, and that which is neither useful nor harmful. This is but another instance in which the practitioner seems to be expected to know everything and do everything. If this presentation has given the general practitioner a glimpse of some of the problems of those who develop new drugs, and if there is anything here that he can extract and use to advantage, then I will feel richly rewarded.

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Although I am indebted to many physicians and investigators who, through the years, have helped to give me an appreciation of the ethical and scientific rules governing experimentation on human beings, I must express special appreciation to Dr. Max S. Sadove, Dr. Walter J. R. Camp, and Dr. Harry F. Dowling for their most valuable guidance, assistance and criticism.

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1958

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 10-13 Municipal Auditorium Cleveland, Ohio

The Comparative Results and Treatment for Cancer of the Rectum

(Dr. Arthur G. Sullivan Memorial Lecture)

C. NAUNTON MORGAN, F.R.C.S.

Surgeon to St. Bartholomew's Hospital, St. Mark's Hospital for Diseases of the Rectum, and to the Hospital for Tropical Diseases, etc., London, England

Among the points that will be discussed are the operability rate, criteria of operability, and the choice of operation, with emphasis on the value of the Trendelenburg-lithotomy position in all operations for cancer of the rectum and the left colon; a method for preventing transplantation of free malignant cells, especially in conservative operations, and its effect on the incidence of local recurrence; and the likely effect of high ligation on the survival rate following combined excision. From a survey of personal cases of carcinoma of the rectum and rectosigmoid, an attempt will be made to assess the comparative survival rates following the operations of combined excision and anterior resection.

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THE PRESENT ROLE OF ORGANIZED GRADUATE MEDICAL CURRICULUMS IN THE TRAINING OF SPECIALISTS

It is now generally recognized that most of the important advances in therapy in the present century have resulted from the judicious application of corresponding advances in the basic medical sciences. One example is the improvement in medical and surgical treatment which resulted from the appreciation and use of the physiologic principles of fluid and electrolyte balance; innumerable others could be cited. Day-to-day application of the basic sciences has become the responsibility of the practicing physician as well as of the clinical investigator. General recognition of this is evidenced by the fact that approximately half of the time spent in undergraduate medical school is devoted to the basic medical sciences.

There now exists the additional need for intensive, concentrated instruction in advanced areas of the basic sciences as they apply to each specialty. The time available in the undergraduate medical curriculum obviously cannot provide either sufficient nuclear physics for the future radiologist or enough details on the physiology of ciliary secretion for the potential ophthalmologist. The American specialty boards have acknowledged this, and practically all of them require inclusion of instruction in the basic sciences as a part of approved residency programs. The immediate question is, how can such instruction be given most effectively?

Since students at the graduate level have acquired previously an extensive general basic and clinical background, the situation is ideal for both integrated instruction in the basic subjects and emphasis on their application. To accomplish this properly requires the combined, closely cooperative efforts of a full basic science and clinical faculty. These principles were stated a good many years ago by Dr. George H. Meeker, founder and first dean of the Graduate School of Medicine, University of Pennsylvania. Largely through his efforts, the Pennsylvania Plan was established in 1916, and consisted of a full year of formal courses in the clinical specialties and in the basic sciences. The standards adopted in 1923 by the

American Medical Association for graduate medical education were based on the same general principles.

For the past 40 years, students of the Graduate School of Medicine have followed essentially this type of program, usually at some stage of their residency training. However, certain practical considerations have restricted its fullest possible utilization. The most important of these is the simple economic fact that the great majority of physicians, after completing their internships, cannot afford to spend an additional year in school prior to or during the residency period. Thus the hospital offering residency training has the primary responsibility for providing specialized training in the basic sciences.

While it can be assumed that all hospitals with approved residency programs have capable clinical staffs in the respective specialties, the majority do not have access to adequate faculties or facilities to present complete, organized courses in the basic sciences. Even in hospitals affiliated with medical schools, the major efforts of the teaching staff are generally directed toward instructing undergraduate students. Furthermore, while in the hospital the resident's primary responsibility is always to his patients; his attendance at classes is contingent on his freedom from calls, and hence is usually irregular.

To fulfill their teaching obligation to their residents, a number of hospitals have followed the practice of sending them to the Graduate School of Medicine for a full academic year. To assist those hospitals which cannot spare the services of residents for this long a period, the school has now established the Two Semester Plan.

Beginning with the academic year 1958 to 1959, the Graduate School of Medicine will offer the 14 courses in the different medical specialties as two semesters of four months each. The first, or basic, semester in each specialty will consist chiefly of instruction in the basic medical sciences as they apply to the specialty, correlated with selected clinical topics in which application of the basic sciences will be emphasized. In addition, students in all specialties will attend the 160 hour correlated basic sciences course, which includes an integrated review of recent developments in biochemistry, immunology, microbiology, pathology, pharmacology, physiology and physical anthropology as they apply to all specialties. In previous years, this course has been presented over the entire academic year.

The basic semester has been designed particularly for incorporation into hospital residency programs. Thus, the hospital might agree to send its residents to the School for the basic semester as a part of a two or three year training program. The resident will receive the benefit of an intensive course in the basic aspects of his specialty. In the succeeding part of his residency, he will be a more active participant in the integrated basic and clinical training which is conducted during the ward rounds and seminars at his hospital. This program presents a solution to the urgent problem of the majority of hospitals which are both eager and obligated to provide specialized instruction in the basic sciences but cannot maintain full basic science faculties.

In the second, or clinical, semester, teaching will be concentrated on applying to the individual specialties the basic material presented in the first semester. The content of the full academic year's courses will, therefore, be essentially the same as those given in the past.

In addition to men already participating in residency training, there are several groups of physicians for whom the opportunity to take a full academic year of study in a specialty is particularly advantageous. These include men who are about to enter specialty training after several years of general practice, medical officers who have just completed a tour of duty in military service, career officers who obtain assignment to a full year's courses, and physicians who come from abroad to study in this country. Doctors from non-English-speaking countries are now required to take an examination in English, administered in their own countries, prior to enrollment. Those who fail to qualify must attend a summer course in English at an American university.

Courses in the dental specialties and in graduate veterinary medicine, given in conjunction with those schools at the University

of Pennsylvania, will continue to be presented as full-year programs.

The Two Semester Plan utilizes to the fullest advantage the specialized teaching facilities of the community hospital and of the University and its affiliated hospitals. It establishes a pattern by which the high standards of basic science training in the specialties can be aligned with those which now exist for undergraduate medical teaching.

GEORGE B. KOELLE
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NEW DISTURBANCES OF THE LUNG

In several medical periodicals, reports recently have been published of unusual conditions affecting the lungs. The pathologic changes are not comparable to those described in the textbooks; the symptomatology resembles that of a variety of inflammations and infections; the laboratory studies yield fungi or negative results, complicated in their interpretation by the previous use of antibiotics. The roentgenologic appearances resemble those of pneumonitis, which in itself is variable.

Bergmann, Flance and Blumenthal[1] of the Jewish Hospital, St. Louis, recently reported two cases of the condition which they characterized as thesaurosis. The term is defined as "a condition resulting from the storing up in the body of unusual amounts of normal or foreign substance." "Thesaurismosis," which is synonymous, is the term preferred by most medical dictionaries. The St. Louis physicians, while not positive, believe that the diffuse bilateral pulmonary infiltrates and hilar lymphadenopathy detected radiographically were due to inhalation of hair spray and that polyvinylpyrrolidone was the substance in the hair spray which probably was responsible. In one case a lymph node was examined, and they concluded that "it is fair to assume that the scalene adenopathy was an accurate reflection of the pulmonary lesion." However, "the exact nature of the particulate matter in the lesion could unfortunately not be determined."

In an effort to decide whether or not the chemical mentioned was responsible, the investigators evaporated some of the hair spray and secured a residue which was then suspended in a saline solution and injected into guinea pigs. Indurations developed in the guinea pigs. Apparently experiments were not made with animals to determine whether or not inhalation of the hair spray as used could produce in the animals' lungs conditions similar to those seen in the two women.

Subsequently, newspapers in Monroe, Louisiana, and the press services reported that a woman died of a lung condition in which microscopic examinations of lung tissue seen at necropsy showed "the air sacs contained cells filled with a peculiar granular material which is believed to represent a reaction of the body to the foreign substance in hair spray."

Dickie and Rankin[2] of the Department of Medicine and the Cardiopulmonary Laboratory, University of Wisconsin, reported on 39 cases of acute granulomatous interstitial pneumonitis, characterized as "farmer's lung," which occurred in agricultural workers in dusty jobs. The roentgenograms showed interstitial pneumonitis; biopsy of the lung revealed inflammation with epithelioid and giant cells, and bacteriologic studies yielded negative results. These investigators believe the condition results from a hypersensitivity response to mold and products of molds occurring in a wide variety of organic material.

In still another article, Rosen, Castleman and Liebow[3] described pulmonary alveolar proteinosis as "a remarkable disease of the lung that consists of the filling of the alveoli by a PAS-positive proteinaceous material, rich in lipid. This material appears to be produced by the lining cells, which slough into the lumen, ultimately becoming necrotic and yielding granules and variable laminated bodies to the alveolar content."

These investigators, who are working at the Central Laboratory for Pathologic Anatomy and Research of the Veterans Administration, the Armed Forces Institute of Pathology, the departments of pathology of Harvard Medical School and the Massachusetts General Hospital, and the Yale University School of Medi-

cine, are convinced that they have discovered a new entity in which the etiologic agent is still obscure. In their paper, which reviewed 27 cases seen during the past five years and increasingly in recent months, the patients varied in age from a boy of two years and four months to a man of 57. There were 15 men and six women among the civilians studied; their occupations were varied. Eight of these patients died, some apparently because proteinaceous material blocked the respiratory surface. The investigators made a most thorough study, using almost every available method to detect the nature of this condition, which, they said, may or may not be heralded by fever. They concluded that nothing is known as yet regarding the etiology of the condition, and they recommended that a search for a causative agent be made by microbiologic, chemical and epidemiologic methods. In some instances secondary fungous infections seem to have occurred. The disease has been detected in all parts of the United States, in Canada, in England, and in Italy.

At present, millions of women in the United States are using hair sprays similar to those alleged to have caused the pathologic changes in the patients whose cases were reported from St. Louis and from Louisiana. Most women use such sprays at most two or three times daily. Beauticians and other workers in beauty shops are obviously exposed constantly during the day to the vapor of hair sprays, yet extensive examinations of such operators have failed to reveal a single instance of a condition such as that reported from St. Louis.

If there is any belief that the occasional inhalation of minimal amounts of polyvinylpyrrolidone can produce such conditions, more positive proof can be obtained by exposing animals to inhalations of minimal amounts of the mist in a dosage similar to that which might be received by any ordinary user. Injecting a residue beneath the skin, as was done in the St. Louis experiments, certainly in no way resembles the conditions which produced lesions of the lung such as were described in the St. Louis cases.

Pathologists would wish to ascertain any similarities that might exist between the conditions seen in St. Louis and Louisiana and those of the cases reported by Rosen and associates. The latter cases came from California, Georgia, Massachusetts and other areas. Intensive bacteriologic and viral studies failed to reveal any specific causative agent. Results of tuberculin, histoplasmin and coccidioidin tests were in most instances normal. The condition most nearly resembles pneumochysis, a disease which has been reported in the past mainly in premature infants. However, every attempt to demonstrate parasites in the condition called alveolar proteinosis has failed. The authors pointed out that some chemical inhalant may be the inciting factor, but that there was no consistency of exposure and the patients concerned were of greatly varying ages and occupations.

Whether the lung conditions here described are actually new and due to some new invading organism such as a virus, a bacterium or a parasite; whether they are associated with some new environmental condition; or whether they represent a change in the tissues resulting from modern therapy such as the antibiotics and sulfonamides cannot at this time be answered. Certainly, however, they represent new pathologic conditions.

Dr. Paul B. Szanto,[4] pathologist of the Cook County Hospital in Chicago, has called my attention to the effects of therapy on the morphologic appearance of an important and frequent pathologic condition affecting the lung. Uremia may be associated with a change in the lung called uremic pneumonitis, characterized by diffuse, rubbery induration of the lung frequently associated with fibrinous pleurisy. In this condition the alveoli contain granular protein precipitate and a large amount of fibrin. The condition has occurred much less frequently recently because of the effective control of the acid-base balance in uremia. The frequency and intensity of the outpouring of fibrin into the alveolar spaces parallel the depression of the carbon dioxide-combining power in the blood.

One wonders whether the conditions seen by Rosen, Castleman and Liebow[3] concern a serous inflammation in which the capillaries of the alveolar septa become permeable for

the serum protein and whether the serous inflammation is due to a chemical toxic compound or a living agent. Possibly the condition may represent what occurs in an ordinary pneumonia when the course and morphologic appearances are changed by chemotherapy.

In the Cook County Hospital two cases have been studied post mortem in which the surgical-pathologic material was practically identical with that seen in the cases described as "farmer's lung" and in which the most careful bacteriologic, mycologic and chemical studies failed to indicate a cause. Neither patient was a farmer; both were city dwellers.

Finally, the conditions called pulmonary proteinosis and "farmer's lung" have some aspects resembling those of beryllium poisoning, which is an entirely new disease resulting from the use of beryllium alloys in the manufacture of fluorescent lights. Obviously the cases described as either proteinosis or "farmer's lung" were in no way related to beryllium. Nevertheless, beryllium poisoning is characterized by an excessive outpouring of edema fluid containing high protein into the alveolar spaces, and chronic beryllium poisoning includes pulmonary granulomatosis and, later, pulmonary fibrosis.

The three reports here noted offer a wide area for extensive investigation by bacteriologists, virologists, roentgenologists, pathologists, epidemiologists and clinicians. The etiology of the conditions observed has not been established with certainty in any of the reports. There are no resemblances to such clear-cut conditions as bacterial or viral pneumonia, tuberculosis, histoplasmosis, moniliasis or other conditions affecting the lung.

In his search for an etiologic agent, the clinician has tried to find some single cause and has fallen into the traps laid by the wide variety of potentially harmful toxic and environmental agents that surround modern living. Conceivably, any condition that might cause localized capillary permeability could produce some of the pathologic and roentgenologic observations that have been recorded. The challenge to the scientific investigators is immediate.

MORRIS FISHBEIN

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"DISEASES OF THE COLON & RECTUM"

THREE issues have now appeared of a new periodical *Diseases of the Colon & Rectum* of which Dr. Louis A. Buie is editor-in-chief. In recent years knowledge of diseases of the colon has accumulated greatly and has been published in a variety of physiologic, internal medical and surgical journals. However, articles also appear in these journals with special emphasis on metabolism, pathology, virology, radiology and cancer. This indicates the need for a special periodical devoted to the colon, rectum and anal canal.

While the journal is sponsored by the American Proctologic Society, it will not be limited to the proceedings of the society but will include the significant papers chosen by the editor from the proceedings as well as contributions volunteered directly. Obviously this makes for a periodical of much higher quality than would result from total publication of any type of proceedings.

The editor apparently has already found, as have others, that the greatest difficulty inheres in publishing verbatim reports of symposia and discussions. Undoubtedly, he will have to take the blue pencil in hand, as have other editors, in order to bring such material into the kind of concrete, grammatical expression that is characteristic of good English writing. The three issues already published indicate that real progress is being made in many of the conditions such as ulcerative colitis, diverticulosis, cancer and allergy in relationship to proctology.

The periodical is published by the J. B. Lippincott Company, Philadelphia.

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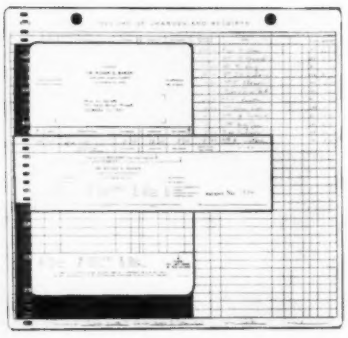

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(Continued on page A-114)

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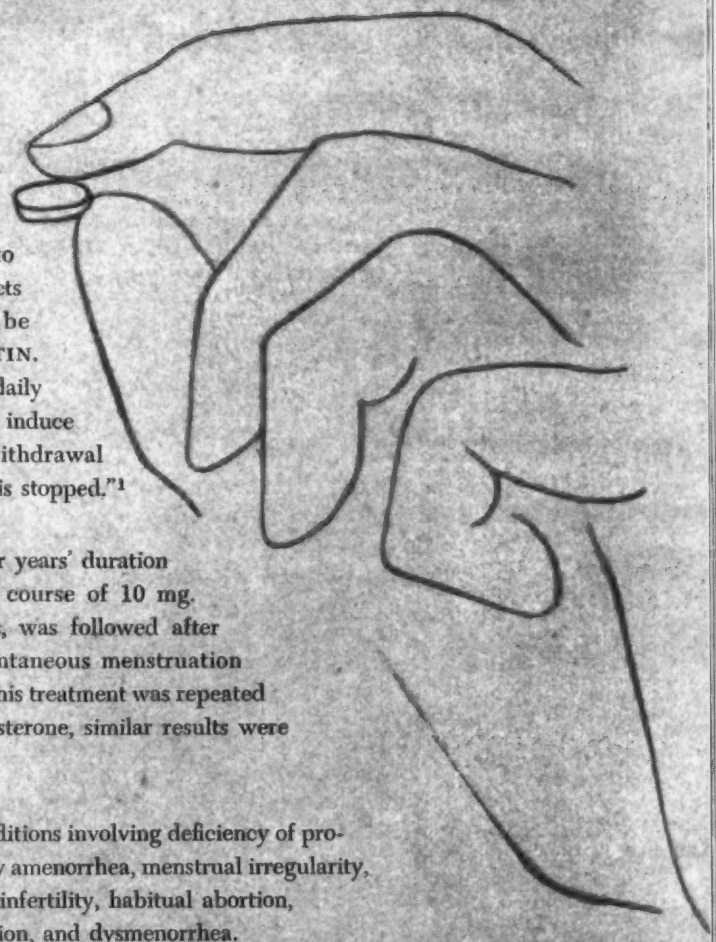

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REFERENCES:
(1) Greenblatt, R. B., & Jungck, E. C.: *J.A.M.A.* 166:1461 (Mar. 22) 1958.
(2) Hertz, R.; Waite, J. H., & Thomas, L. B.: *Proc. Soc. Exper. Biol. & Med.* 91:418, 1956.

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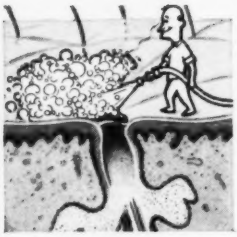

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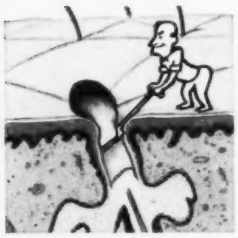

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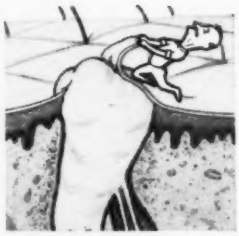

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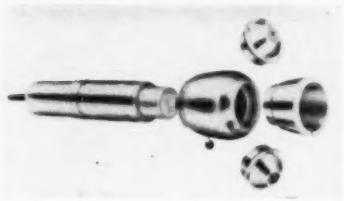

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(Continued on page A-116)

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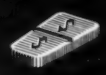

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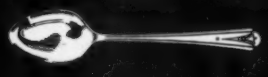

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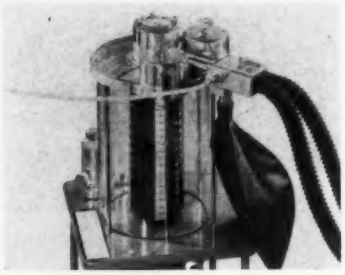

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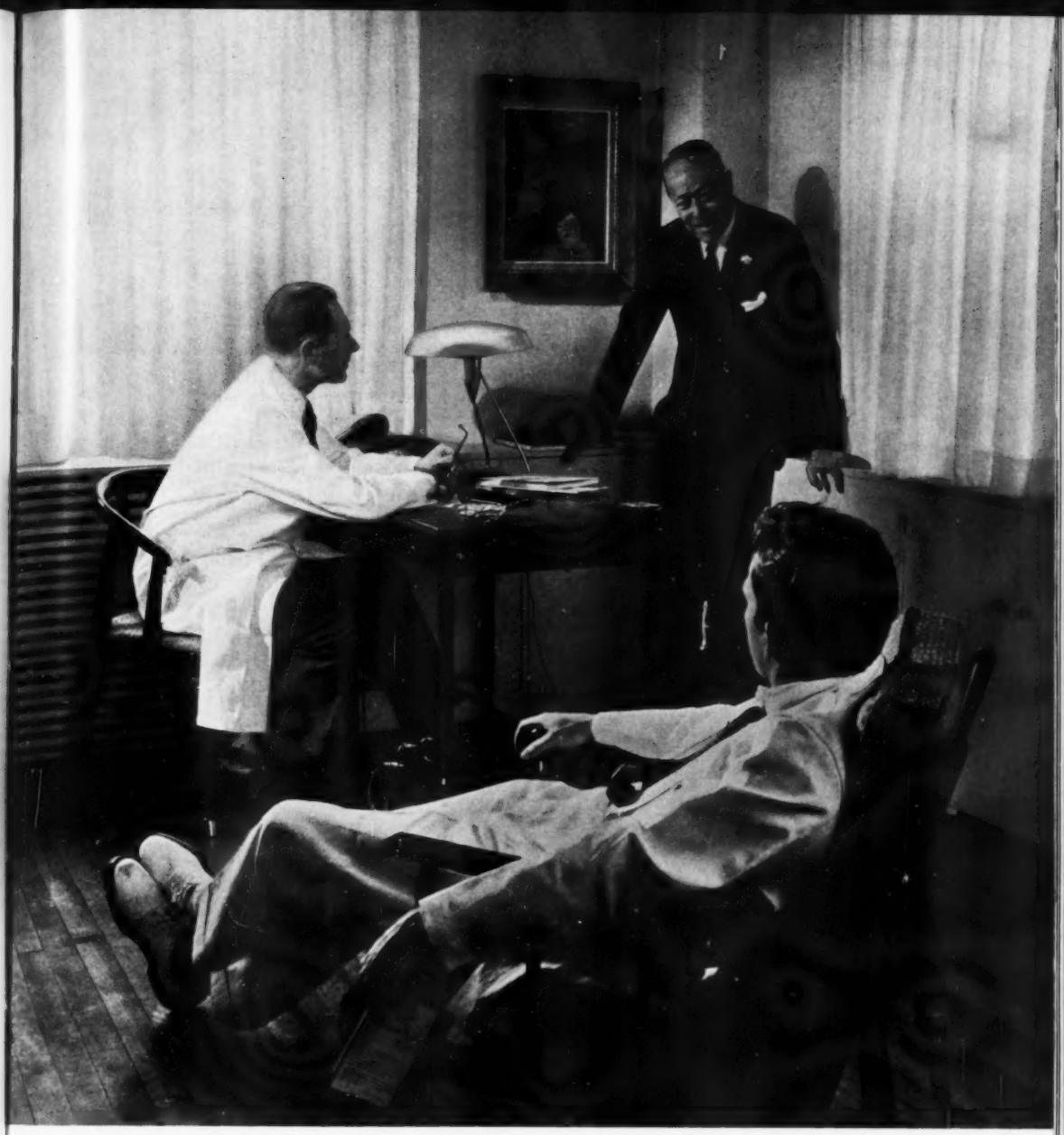

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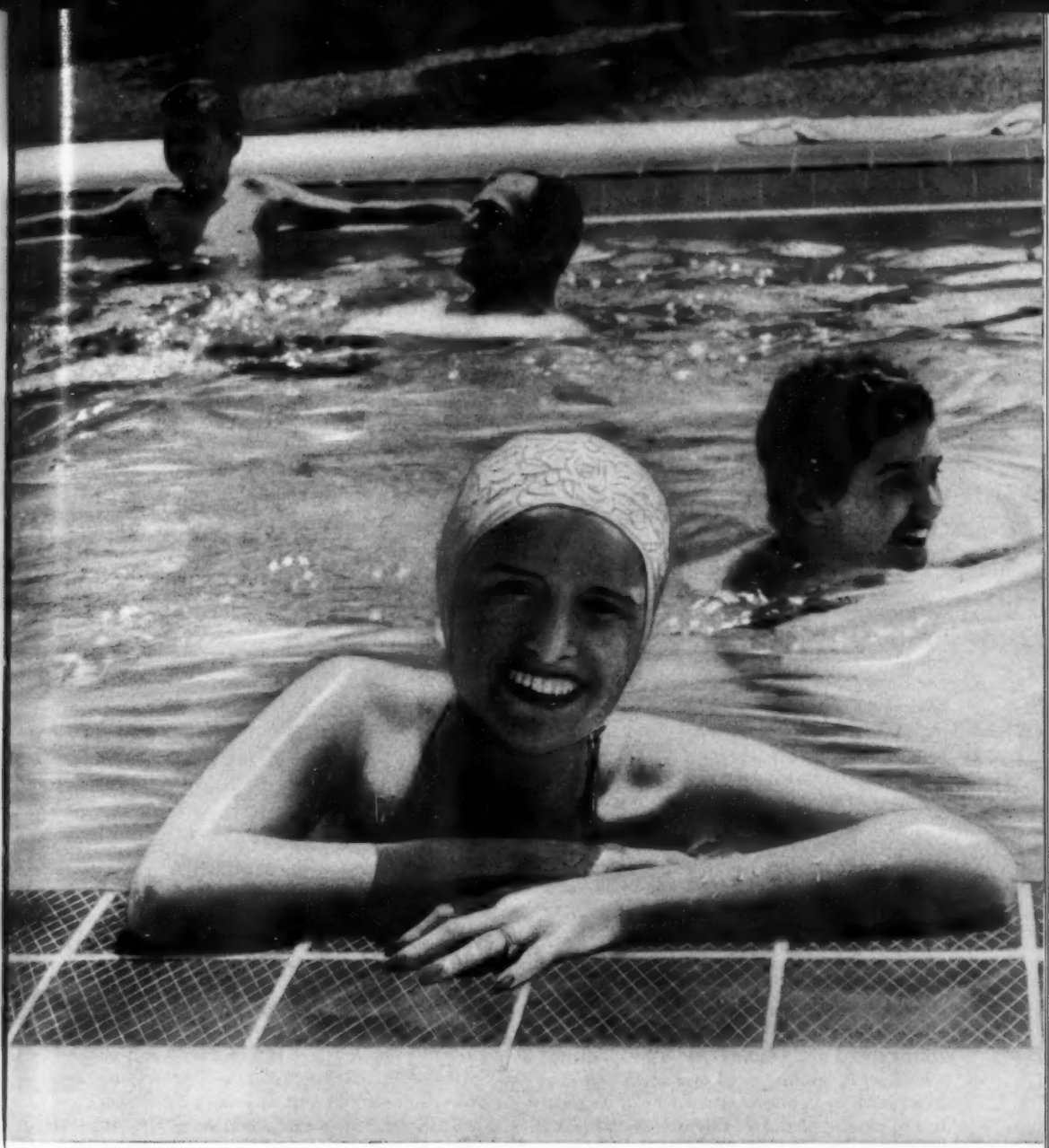
(Continued on page A-120)



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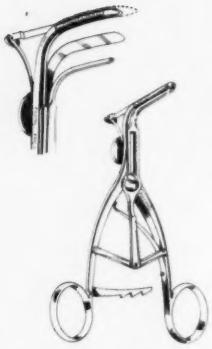

• **SALVATORE-MALONEY EMERGENCY TRACHEOTOME**

DESCRIPTION: For use in an emergency tracheotomy through either the cricothyroid membrane or the upper tracheal rings, this instrument has a sharp knife blade which is attached to one of the instrument blades and can be advanced or retracted as desired by manipulating a finger lever. Trauma to soft tissue thus is avoided and the blade can be reserved for cutting through cartilage. Equipped with three blunt-tipped blades, the instrument is a three direction spreading device which provides a swift, safe method of introducing a tracheotomy tube.
CAUTION: The instrument should not be used in a low tracheotomy when excess tissue such as goiter, tumor, edema or obesity exists anterior to the tracheal rings.
PRODUCER: George P. Pilling & Son Company, Philadelphia.

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DESCRIPTION: Claimed to be accurate even in atmospheres of 100 per cent relative humidity, this unit is styled like a table clock and supplied with a hook so it can be placed over a support bar in an oxygen, open-top or croup tent or incubator. It also can be placed in rooms in which the patient's condition requires accurate checking of humidity levels and used in operating rooms where high humidity is desired to decrease the possibility of static electricity. The sensing element is a slender strand of specially treated nylon fiber, described as more responsive to slight humidity changes than a human hair element. Accuracy of its response is unaffected by sprayed medicaments.
PRODUCER: National Cylinder Gas Division of Chemetron Corporation, Chicago.

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PRODUCER: Abbott Laboratories, North Chicago.

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1. Batterman, R. C.; Grossman, A. J.; Mouratoff, G. J., and Leifer, P.: A Clinical Re-evaluation of Daytime Sedatives, Scientific Exhibit presented at AMA Convention, San Francisco, June 23-27, 1958.

2. Grossman, A. J.; Batterman, R. C., and Leifer, P.: Fed. Proc. *17*:373 (March) 1958.

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News of Interstate

Charles F. Kettering
Assembly Dinner Speaker

SCIENTIST, inventor and friend of medicine, Charles F. Kettering will receive a citation commemorating his outstanding achievements and his significant contributions to the medical field at the annual dinner of the Interstate Postgraduate Medical Association, Wednesday, November 12, in Cleveland. Mr. Kettering will also present the address of the evening: "An inventor looks at science and medicine."

CHARLES F. KETTERING

Evening Sessions

For the convenience of physicians attending the Assembly, the Monday and Tuesday evening sessions will be held at the centrally located Statler-Hilton Hotel. The daytime meetings, exhibits and motion pictures will all be at the Cleveland Auditorium.

Highlighting the evening program, Monday, November 10, will be an illustrated lecture on "Man, stress and motion," by Colonel John P. Stapp, leader in aviation medicine. Colonel Stapp has received international recognition for his work on severe stress caused by the deceleration experienced by fliers when the speed of their planes exceeds that of sound. An important aspect of the management of trauma will be covered by Lieutenant Colonel H. Haskell Ziperman, Brooke Army Medical Center, Fort Sam Houston, Texas, in an illustrated address on "Wound debridement."

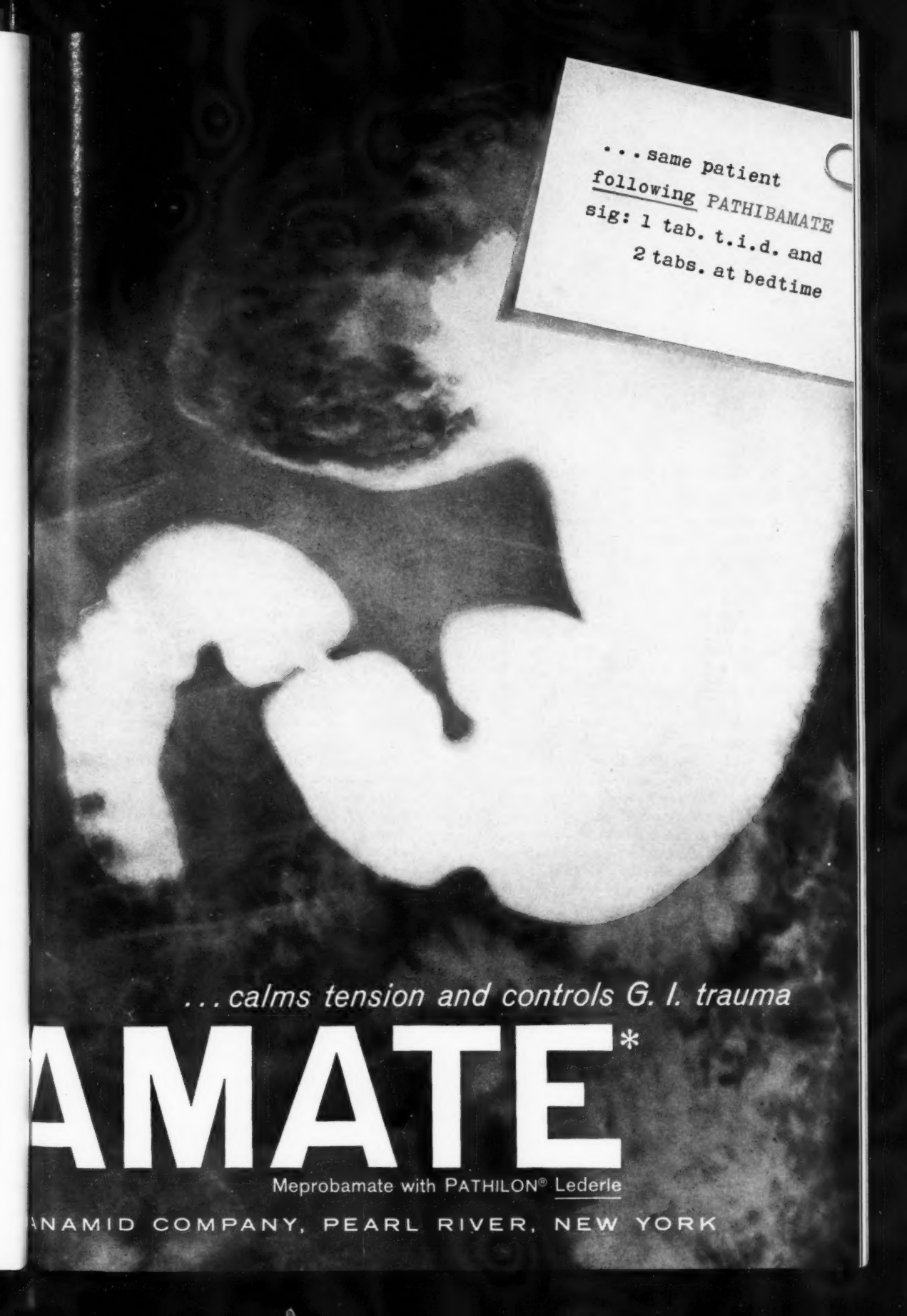
On Tuesday evening, November 11, the program will feature discussions on "Problems in abdominal surgery," by Drs. Waltman Walters and George Hallenbeck, Mayo Clinic, Rochester, Minnesota; "The tired mother syndrome," by Dr. Leonard L. Lovshin, Cleveland Clinic, Cleveland; and the Arthur G. Sullivan Memorial Lecture, "The comparative results and treatment for cancer of the rectum," by Mr. C. Naunton Morgan, London, England.

Following the Tuesday evening lectures, there will be a special program of music and dancing in the ballroom of the Statler-Hilton Hotel. The Interstate trustees are offering this entertainment without charge to all physicians and their wives at the meeting.

Women's Special Events

Several special events have been scheduled for the wives of physicians attending the Assembly. From 2 to 4 P.M. Monday, November 10, wives of the Interstate trustees and officers and officers of the Auxiliary to the Cleveland Academy of Medicine will be hostesses at a hospitality tea in the Pine Room of the Statler-Hilton Hotel. At 1 P.M. Tuesday, November 11, a luncheon and style show will be held at the Higbee Company department store. Tickets will be on sale at the Statler-Hilton Hospitality Center until 10 A.M. Tuesday. Arrangements have been made for a special matinee performance of a well-known play at the Cleveland Playhouse Wednesday, November 12, to be followed by a tea to meet the play's cast. Tickets will be available at the Hospitality Center until Wednesday morning.

Wives are also particularly invited to the special program Tuesday evening and to the Wednesday banquet, and they will be welcome at all the lectures and the exhibits.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THE MEDICAL Bookman

► HIGH ARTERIAL PRESSURE

By F. H. Smirk, M.D., Professor of Medicine, University of Otago, Dunedin, New Zealand. 764 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $15.00.

As one of the most complete and up-to-date works on hypertension, this text covers all aspects of the subject, with particular emphasis on physiology, pathogenesis, pharmacology and treatment.

The author has reviewed the literature extensively, tying together references to the original papers in chapters which are extremely easy to follow. Although he has emphasized recent developments, he has also described historical aspects of the various phases of hypertension.

The bulk of the original observations and clinical data has been gathered by a medical team headed by the author, and the plan of therapy presented is based on the observed responses of over 500 patients treated with hypotensive drugs.

Various chapters deal with blood pressure and its measurement, natural history and ecology of high and low blood pressure, clinical manifestations and etiology, psychosomatic aspects, physiology of pressure regulation, experimental hypertension, essential hypertension, and prognosis.

The section on treatment stresses pharmacology as well as general principles and the rationale for therapy. Discussions are included on surgical treatment; salt restriction; use of hypotensive drugs, *Rauwolfia* alkaloids and ganglion-blocking agents; combined treatment; and results. These are illustrated by tables and electrocardiogram and x-ray reproductions.

Y. S.

► DIAGNOSTIC MEDICAL PARASITOLOGY

By Edward K. Markell, M.D. and Marietta Voge, Ph.D., Assistant Professors of Infectious Diseases, Division of Parasitology and Tropic Diseases of the University of California School of Medicine, Los Angeles. 276 pages with 115 illustrations, 5 in color. 1958, W. B. Saunders Company, Philadelphia and London. $7.00.

Here is a brand-new textbook in a field that is not understood too well by the average medical student. The book has been designed so that it may be used for teaching parasitology as an independent course or integrated with the teaching of the organ systems affected by various infectious agents.

Subjects discussed in the 14 chapters include parasites, parasitism and host relations; procedures in examination of stool specimens; intestinal protozoa and helminths; procedures in examination for blood parasites; malaria; other blood parasites, hemoflagellates and filariae; parasites of the genitourinary tract and the tissue; arthropods and human disease; pseudoparasites and pitfalls; special diagnostic methods; and fixatives, stains and commonly used procedures.

There is a rather meager list of references but a good index. The figures are clear and sufficient in number to illustrate the subjects discussed.

Students, clinical pathologists, medical technologists and clinicians will find this a very readable addition for their library.

A. H. S.

(Continued on page A-150)

In Peptic Ulcer... ONE, All-Purpose Formula

ALUDROX SA benefits the peptic-ulcer patient by providing complete medical management in one preparation. It relieves his pain, reduces his acid secretion, calms his emotional distress, promotes ulcer healing.

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Peptic ulcer	Cardiac arrhythmias
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Edited by Walter Modell, M.D.
Written by 37 Eminent Contributors

Unlike any other book published, DRUGS OF CHOICE 1958-1959 is the only book available today that not only critically reviews drugs in current use, but, more importantly explains the basis for choosing one over another. The first in a series of biennial volumes, this 931 page reference answers questions like those above; furthermore, it can be a practical guide to all of your therapeutic decisions.

This book compares drugs within therapeutic groups in realistic and practical terms covering relative potency, toxicity, modes of administration, speed of development of action and duration and indicates which of the newer drugs are superior to the old. Practical advantages of one drug over another are shown even though both exert similar or even identical pharmaco-dynamic actions.

Edited by Dr. Walter Modell, a leading clinical pharmacologist, and written by 37 recognized experts who expressed their unbiased opinions on the most highly successful drugs in current use in the particular specialty based on their own specialized knowledge or experience, this is a book that can guide you from your diagnosis to the preferred treatment. An alphabetically-arranged Drug Index at the end of each chapter lists commonly used drugs by generic names and by proprietary names when practical.

Edited by WALTER MODELL, M.D., Associate Professor of Pharmacology, Cornell University Medical College; Attending Physician, New York Veterans Administration Hospital; Associate Visiting Physician, Bellevue Hospital, New York, New York; with 37 eminent contributors. 1958, 931 pages, 6¾" x 9¾", illustrated. Price, $12.75.

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► FOUNDATIONS OF NEUROPSYCHIATRY

By Stanley Cobb, M.D., Bullard Professor Emeritus of Neuropathology, Harvard Medical School, Boston. Ed. 6. 313 pages, illustrated. 1958, The Williams & Wilkins Company, Baltimore. $5.00.

First published in 1936 under the title "A Preface to Nervous Disease," this book has been brought up to date and incorporates many of the newer concepts regarding the function of the nervous system, neurophysiology and neurochemistry.

A highly respected author and investigator and emeritus professor of neuropathology at Harvard Medical School, Dr. Cobb has by no means limited his interests to pathology, as is evidenced in this work. However, since his orientation is primarily in the neurologic sciences, he has devoted most of the book to basic neurology. Discussions on neuroanatomy and neuropathology are comprehensive, clear and not too detailed.

The chapters on psychiatry necessarily condense too much into too little space and contain only the most general principles of the psychologic concepts in medicine and psychopathology. The author was an early exponent of the monistic approach to medicine and does not adhere to the strictly organic or psychologic viewpoint; his discussion on the thorny problem of pain best illustrates this approach.

E. M. L.

► A PRIMER OF CEREBRAL PALSY

By Joseph D. Russ, M.D., Assistant Professor of Pediatrics, and Hyman R. Soboloff, M.D., Assistant Professor of Orthopedics, Tulane University School of Medicine, New Orleans. American Lecture Series. 77 pages with 16 illustrations. 1958, Charles C Thomas, Springfield, Illinois. $4.00.

The authors have presented in brief and readable form the main points of our knowledge of the etiology, diagnosis and treatment of cerebral palsy. The emphasis on treatment is concerned with the "cerebral palsy team." Therapy is discussed very briefly from the viewpoints of the orthopedist, the pediatrician and the psychiatrist, as well as from those of physical, occupational and speech therapists, teachers and nurses.

H. M. K.

(Continued on page A-152)

Comments by investigators on

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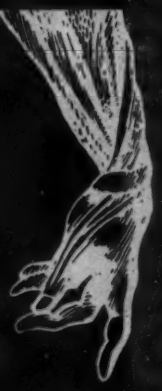

– the remarkably efficient skeletal muscle relaxant, unique in chemical formulation, and outstanding for sustained action and relative freedom from adverse side effects.

PUBLISHED REFERENCES: 1. Carpenter, E. B.: Southern Medical Journal 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Little, J. M., and Truitt, E. B., Jr.: J. Pharm. & Exper. Therap. 119:161, 1957. 4. Morgan, A. M., Truitt, E. B., Jr., and Little, J. M.: J. Am. Pharm. Assn., Sci. Ed. 46:374, 1957. 5. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 6. Park, H. W.: J.A.M.A. 167:168, 1958. 7. Truitt, E. B., Jr., and Patterson, R. B., Proc. Soc. Exper. Bio. & Med. 95:422, 1957. 8. Truitt, E. B., Jr., Patterson, R. B., Morgan, A. M., and Little, J. M.: J. Pharm. & Exper. Therap. 119:189, 1957.

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CONDITION	NO. PATIENTS	RESPONSE			
		"marked"	moderate	slight	none
STUDY 1[1]					
Skeletal muscle spasm secondary to acute trauma	33	26	6	1	—
STUDY 2[2]		"pronounced"			
Herniated disc	39	25	13	—	1
Ligamentous strains	8	4	4	—	—
Torticollis	3	3	—	—	—
Whiplash injury	3	2	1	—	—
Contusions, fractures, and muscle soreness due to accidents	5	3	2	—	—
STUDY 3[5]		"excellent"			
Herniated disc	8	6	2	—	—
Acute fibromyositis	8	8	—	—	—
Torticollis	1	—	—	1	—
STUDY 4[6]		"significant"			
Pyramidal tract and acute myalgic disorders	30	27	—	2	1
TOTALS	138	104 (75.3%)	28 (20.3%)	4	2

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"In the author's clinical experience, methocarbamol has afforded greater relief of muscle spasm and pain for a longer period of time without undesirable side effects or toxic reactions than any other commonly used relaxants . . ."[2]

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"An excellent result, following methocarbamol administration, was obtained in all patients with acute skeletal muscle spasm."[5]

THE JOURNAL of the American Medical Association

"In no instance was there any significant reduction in voluntary strength or intensity of simple reflexes."[6]

Southern Medical Journal

"This study has demonstrated that methocarbamol (Robaxin) is a superior skeletal muscle relaxant in acute orthopedic conditions."[1]

► SURGERY OF THE BILIARY TRACT, PANCREAS & SPLEEN
A Handbook of Operative Surgery

By Charles B. Puestow, M.D., Clinical Professor of Surgery, College of Medicine and Graduate College, University of Illinois, Chicago. Ed. 2. 381 pages, illustrated. 1957, The Year Book Publishers, Inc., Chicago. $9.75.

In the preface to the first edition of this book, the author pointed out that he was preparing a handbook for trained surgeons and for surgical residents. His purpose was to provide concise instruction in less well-known procedures for the practicing surgeon, not to offer a guide for the occasional or would-be operator. Again he has accomplished this mission well and, in addition, has presented an excellent review of the more common surgical problems of this region, notably those of the gallbladder and common bile duct.

The liver, the extrahepatic biliary system, the pancreas and the spleen are discussed in separate sections. Each contains a brief but accurate review of the pertinent anatomy and physiology, an outline of surgical diseases of the particular organ or organs, and clearly described methods of treatment. Uncluttered illustrations greatly enhance these descriptions. Most of the material presented is well accepted, but when a controversial point is raised the author acknowledges the opinion offered as his own.

The section on the liver presents a concise outline of the various liver function tests and their use. Management of abscesses and cysts is discussed and illustrated, as well as the indications for and technic of liver biopsy. Technic of hepatic resection also is briefly outlined, but the more recent work on intrahepatic anatomy and its application is not. The direct, factual approach which makes this book valuable is evident in the section on surgical lesions of the gallbladder and bile ducts. Particularly worthwhile are the discussion and illustration of the management of common duct injuries and strictures.

Some of the newer ideas regarding the treatment of chronic pancreatitis have been added in this edition, and disadvantages of each are pointed out. The author seems to have most confidence in the retrograde drainage procedures, but remarks that all the new technics he describes probably are palliative. Pancreatic trauma, cysts and neoplasm also receive attention. Indications and contraindications for splenectomy are presented in tabular form, accompanied by a review of anatomy and physiology, a brief discussion of diseases favorably affected by splenectomy, and a well-illustrated section describing the technic of splenectomy.

D. W. S.

► THE MANAGEMENT OF CHILDHOOD ASTHMA

By Frederic Speer, M.D., Assistant Clinical Professor of Pediatrics, University of Kansas School of Medicine, Kansas City. 116 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $4.75.

The clinical management of asthma in children presents many problems in recognition, differential and etiologic diagnoses and treatment. No one scheme of management is universally successful; hence, experiences and practice vary with each pediatric allergist. The author presents his methods of management in a brief and well-written text.

He wisely emphasizes the need for the physician to educate the parents of children with asthma regarding the chronic nature and the investigation and treatment of the disease. Accuracy of diagnosis, perspective in skin testing, importance of history taking, need for hydration in treatment, dangers of excessive sedation and morphine, and essentiality of environmental control are some of the points stressed. The proper restriction of ACTH and cortisone to the status of a reserve means of treatment is emphasized. The section on the biologic relationships of foods is worthwhile, and the final chapter contains some practical advice on "allergic cookery."

As reflected in the text, cases of children who have food allergy seem to have been especially numerous in the author's clinical experience. He covers the emotional aspects of asthma too briefly, and limits his discussion of pollen and mold factors to those of importance in the Kansas City area. No factual data are presented to support the value of therapeutic hyposensitization.

This small volume will be of interest and aid to any physician who has children in his practice, but it should not be the only source to which he may turn for help in managing childhood asthma.

G. B. L.

(Continued on page A-154)

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► PHARMACOLOGY IN MEDICINE
A Collaborative Textbook

Edited by Victor A. Drill, M.D., Lecturer in Pharmacology, Northwestern University Medical School, Chicago. Ed. 2. 1,243 pages, illustrated. 1958, The Blakiston Division, McGraw-Hill Book Company, Inc., New York, Toronto and London. $19.50.

This revision continues the policy of collaborative authorship established in the original edition of this excellent text, which appeared in 1954. Subsequent developments in drug therapy up to the new publication date are well represented by the inclusion of new agents, and by discussions leading to a fuller understanding of many drugs previously included. Readability is enhanced by the excellent format, the clarity of type and the quality of paper used. Pages are numbered consecutively, a distinct improvement over the previous system of separate pagination by chapters.

Effective revision has been accomplished with little increase in the volume's length. Each chapter heading now bears the name of its author. New to this second edition are an excellent chapter on "Psychopharmacology" and an "Addendum" describing the diuretic and antihypertensive actions of chlorothiazide (DIURIL®). Under "Addenda" in future revisions, the editor plans to continue the addition of up-to-date information on drugs appearing too late for inclusion in the body of the text.

The extensive scope of the revision is indicated by a review of the 87 chapters included in the original edition and by the large increase in the number of references. Reflecting current interest, the increase is especially great in the chapters on local anesthetics; sedatives and hypnotics; alcohols; analgesics; autonomic blockading agents; antihypertensive drugs; electrolytic, fluid and acid-base balances; lipid metabolism; the thyroid gland; the adrenal cortex; agents inhibiting normal and neoplastic blood cell formation, and the new antibiotics. A new chapter, "Drugs affecting behavior," is in keeping with the rapid growth of information and interest in this area. Indicative of this rapid development is the observation that in the original text of four years ago chlorpromazine was described under "Antiemetics," reserpine was described under "Drugs in hypertension," and 5-hydroxytryptamine (serotonin) was not included. This chapter traces briefly the development of psychopharmacology as a field of study—that is, the evaluation of drugs whose principal effects in therapeutic doses are observed in behavioral changes. Acetylcholine, epinephrine and levarterenol (norepinephrine) are discussed in relation to the transmission of nerve impulses in the central nervous system; and current information on lysergic acid diethylamide and 5-hydroxytryptamine is well summarized. Under the headings "Psychomotor stimulants" and "Tranquilizers" are well-written descriptions of drugs modifying behavior.

In general, the authors have continued to emphasize the newer and more effective drugs, devoting less attention to the older drugs which are of decreasing clinical interest. This policy both enhances the value of the text as a basis for current therapeutic applications and reduces its usefulness as a reference source for other purposes.

F. T. M.

► ROENTGENOLOGY OF THE CHEST

Edited by Coleman B. Rabin, M.D., F.C.C.P., Attending Physician and Associate Radiologist for Chest Diseases, The Mount Sinai Hospital, New York, with 50 contributors. 484 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $19.50.

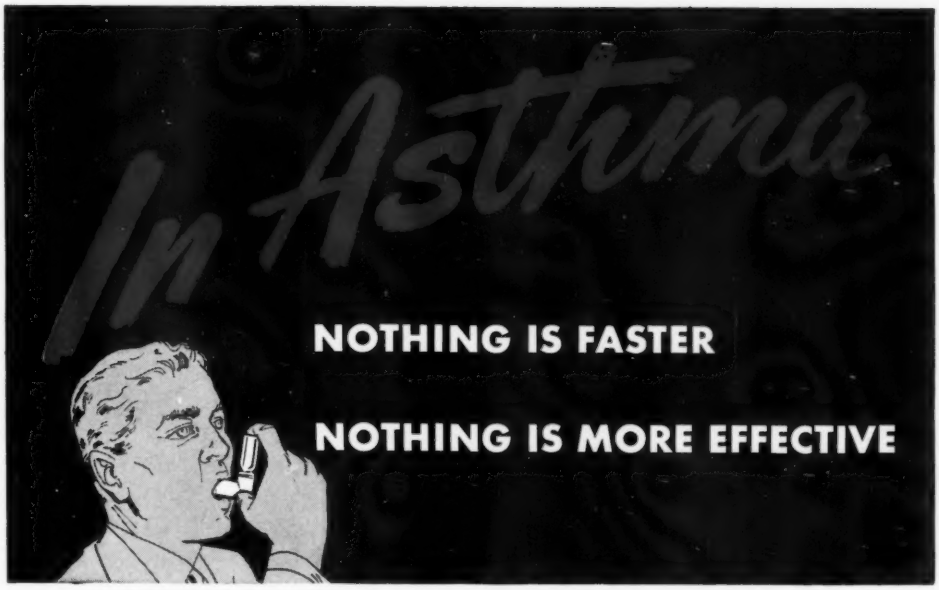
Written for both the clinician and the radiologist, this book was sponsored by the American College of Chest Physicians. The subject matter is all-inclusive, ranging from anatomy and physiology through congenital changes, tumors and inflammatory, cardiovascular and technical findings in the chest.

As one might anticipate, with so many different contributors, the individual sections are not consistent in quality, but on the whole they are extremely well done. Likewise, while one cannot expect exhaustive discussions of each entity in a compendium, the coverage of each subject is good. Many of the individual contributors are acknowledged specialists in the fields which they discuss.

The text is well planned and illustrated and the quality of the prints is excellent. Many of the lists of references will be useful as sources for further study of the subjects.

S. B. F.

(Continued on page A-156)



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LOS ANGELES

► FUNCTIONAL BRACING OF THE UPPER EXTREMITIES

Written and illustrated by Miles H. Anderson, Ed.D., Director, and edited by Raymond E. Sollars, Associate Director, Prosthetics Education Project, University of California School of Medicine, Los Angeles. 463 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $9.50.

Although this interesting volume was prepared as a textbook for paramedical personnel, the author intends also that it serve as a guide for practicing orthotists, prosthetists, occupational therapists, physiotherapists, physiatrists, orthopedic surgeons, rehabilitation specialists and other persons interested in the problem of rehabilitation and in bracing of the upper extremity. The initial chapter, which deals with functional anatomy of the hand, is geared more to the paramedical reader than to the physician. At the same time, the ideas expressed and the illustrations and subject matter are so organized and presented as to form a good reference for anyone interested in anatomy of the hand and upper extremity.

The anatomic concepts established are carried over to the discussion of functional assistive hand splints. Every such splint is shown in excellent photographs and line drawings, with well-illustrated step-by-step directions for constructing it in the home workshop; arm braces are presented in a similar way. Other sequences of illustrations show the proper fitting of the braces.

E. W. J.

► RECONSTRUCTIVE AND REPARATIVE SURGERY

By Hans May, M.D., Associate Professor of Surgery, Graduate School of Medicine, University of Pennsylvania, Philadelphia. Ed. 2. 1,115 pages with 1,030 illustrations, 55 in color. 1958, F. A. Davis Company, Philadelphia. $30.00.

Most of the illustrations in this new edition of a well-known work are from the private practice of the author and his associates. They are interspersed throughout the text to illustrate the various problems encountered in a general plastic surgical practice.

The book has five divisions. The first is given over to the general principles of plastic surgery to acquaint the reader with the various types of free grafts and pedicle flaps, treatment of wounds and wound healing, and the management of major and minor burns. The second division involves problems associated with the head and neck and presents considerable detail in respect to each of the areas in question: the cheeks, lips, nose, eyelids, ears and facial bones. Following a discussion concerning the trunk, the extremities are considered, problems of the hands and feet being presented separately. The last division is devoted entirely to 170 illustrative cases.

Throughout the book, a very comprehensive bibliography on each subject is appended to each chapter, and in the text the surgical technic for the various procedures is well set forth.

J. K. M.

► MODERN TRENDS IN GASTROENTEROLOGY

Edited by F. Avery Jones, M.D., Physician, Central Middlesex Hospital, London, England, with 39 contributors. Ed. 2. 439 pages, illustrated. 1958, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. $16.00.

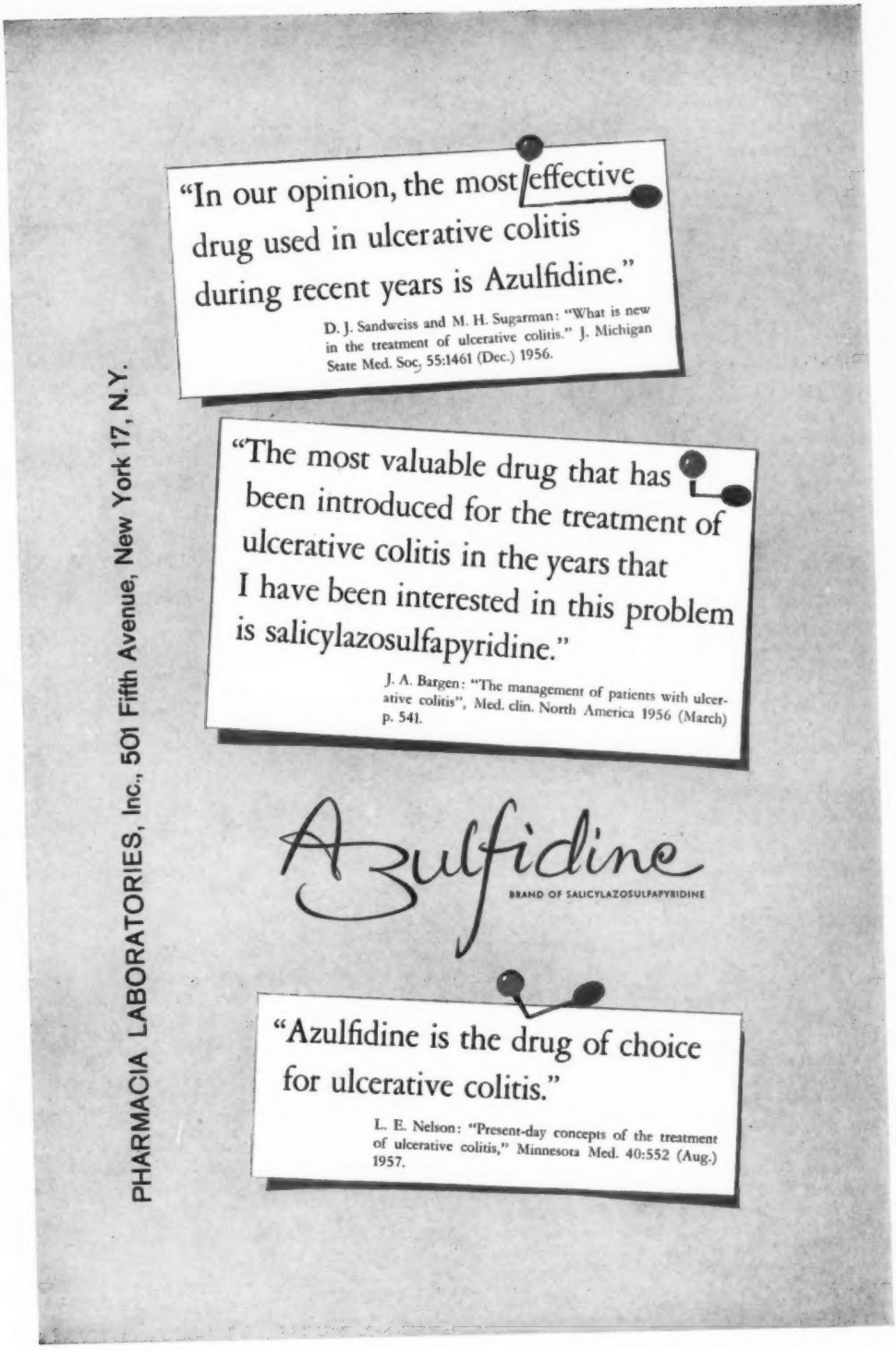
To present the considerable progress made recently in this field, the second volume in this series has been compiled. The first appeared in 1952. Each contributor was chosen because of a particular addition he has made to this field.

New material is especially noted in the introduction, which contains some newer concepts on intestinal motility explained in terms of membrane potentials and potassium exchange, and in the sections dealing with peptic ulcer and with surgical problems relating to the blind loop syndrome and the effects of massive resection of the intestine. In the discussion on antibiotics, the dangers of their use are emphasized over their therapeutic values, reflecting recent discoveries relating to the indiscriminate use of antibiotics. The long section on cancer of the alimentary tract also contains some new ideas.

Other discussions cover the corticosteroids and their present application in certain gastrointestinal diseases, the collagen diseases, columnar epithelium of the lower esophagus, regulation of gastric emptying and acidity, regional ileitis, chronic ulcerative colitis, advances in roentgenology of the biliary tree, liver function and failure, and investigation of pancreatic dysfunction.

Y. S.

(Continued on page A-158)


"In our opinion, the most effective drug used in ulcerative colitis during recent years is Azulfidine."
D. J. Sandweiss and M. H. Sugarman: "What is new in the treatment of ulcerative colitis." J. Michigan State Med. Soc. 55:1461 (Dec.) 1956.
"The most valuable drug that has been introduced for the treatment of ulcerative colitis in the years that I have been interested in this problem is salicylazosulfapyridine."
J. A. Bargen: "The management of patients with ulcerative colitis", Med. clin. North America 1956 (March) p. 541.
Azulfidine
BRAND OF SALICYLAZOSULFAPYRIDINE
"Azulfidine is the drug of choice for ulcerative colitis."
L. E. Nelson: "Present-day concepts of the treatment of ulcerative colitis," Minnesota Med. 40:552 (Aug.) 1957.
PHARMACIA LABORATORIES, Inc., 501 Fifth Avenue, New York 17, N.Y.

► THE MEDICAL MANAGEMENT OF CANCER

By Henry D. Diamond, M.D., Associate Attending Physician, The Medical Neoplasia Service of the Department of Medicine, The Memorial Center for Cancer and Allied Diseases, New York. 179 pages, illustrated. 1958, Grune & Stratton, Inc., New York and London. $6.75.

In the modern concept of cancer management, the nonsurgical methods of treatment are considered to be as important as the surgical methods. This monograph presents briefly but perfectly adequately the role played by the internist in the active treatment of cancer.

The author has divided the carcinomas into two groups: malignancies for which nonoperative management is the primary treatment—Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma, the leukemic group of diseases, and plasma cell myeloma; and malignancies for which surgical intervention is the primary therapy, although medical treatment is of value—neuroblastoma and cancer of the lung, thyroid, ovary, breast and prostate. The internist assumes the active role in treating this latter group when cancer recurs after definitive surgery or when it is so extensive that surgery is contraindicated.

After a brief description of the natural course and behavior of each tumor considered, the author discusses in detail the dosage, mode of action and side reactions of chemical agents and the dosage of x-ray. He also presents statistical data on the incidence and results of untoward reactions. The appendix to the monograph contains a description of the intracavitary uses of radioisotopes.

Emphasis throughout is placed on the tumor and its behavior in the medical management of the cancer patient.

Y. S.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers are reviewed more extensively.

Variables Related to Human Breast Cancer. By V. Elving Anderson, Assistant Director, Dight Institute for Human Genetics, Harold O. Goodman, Assistant Geneticist, Bowman Gray School of Medicine, Winston-Salem, North Carolina, and Sheldon C. Reed, Director, Dight Institute for Human Genetics, University of Minnesota, Minneapolis. 172 pages. 1958, University of Minnesota Press, Minneapolis. $4.00.

Physics for the Anaesthetist; Including a Section on Explosions. By Sir Robert Macintosh, M.D., Nuffield Professor of Anaesthetics, University of Oxford, William W. Mushin, F.F.A.R.C.S., Professor of Anaesthetics, Welsh National School of Medicine, Cardiff, Wales, and H. G. Epstein, Ph.D., First Assistant, Nuffield Department of Anaesthetics, University of Oxford, Oxford, England. Ed. 2. 443 pages with 379 illustrations. 1958, Charles C Thomas, Springfield, Illinois. $15.50.

Cleft Palate and Speech. By Muriel E. Morley, M.Sc., Speech Therapist-in-Charge of the Speech Therapy Unit, United Newcastle upon Tyne Teaching Hospitals, Newcastle upon Tyne, England. Ed. 4. 271 pages with 86 illustrations. 1958, The Williams & Wilkins Company, Baltimore. $6.50.

The Cerebrospinal Fluid; Production, Circulation and Absorption. Ciba Foundation Symposium. Edited by G. E. W. Wolstenholme, O.B.E. and Cecilia M. O'Connor, B.Sc. 335 pages with 141 illustrations. 1958, Little, Brown & Company, Boston. $9.00.

Regional Ileitis. By Burrill B. Crohn, M.D., Consulting Gastroenterologist, and Harry Yarnis, M.D., Associate in Medicine for Gastroenterology, Mount Sinai Hospital, New York. Ed. 2. 239 pages with 81 illustrations. 1958, Grune & Stratton, Inc., New York and London. $7.25.

Memoirs of a Golden Age. By Maurice Davidson, London, England. 140 pages with 29 illustrations. 1958, Basil Blackwell & Mott, Limited, Oxford, England. Distributed by Charles C Thomas, Springfield, Illinois. $3.75.

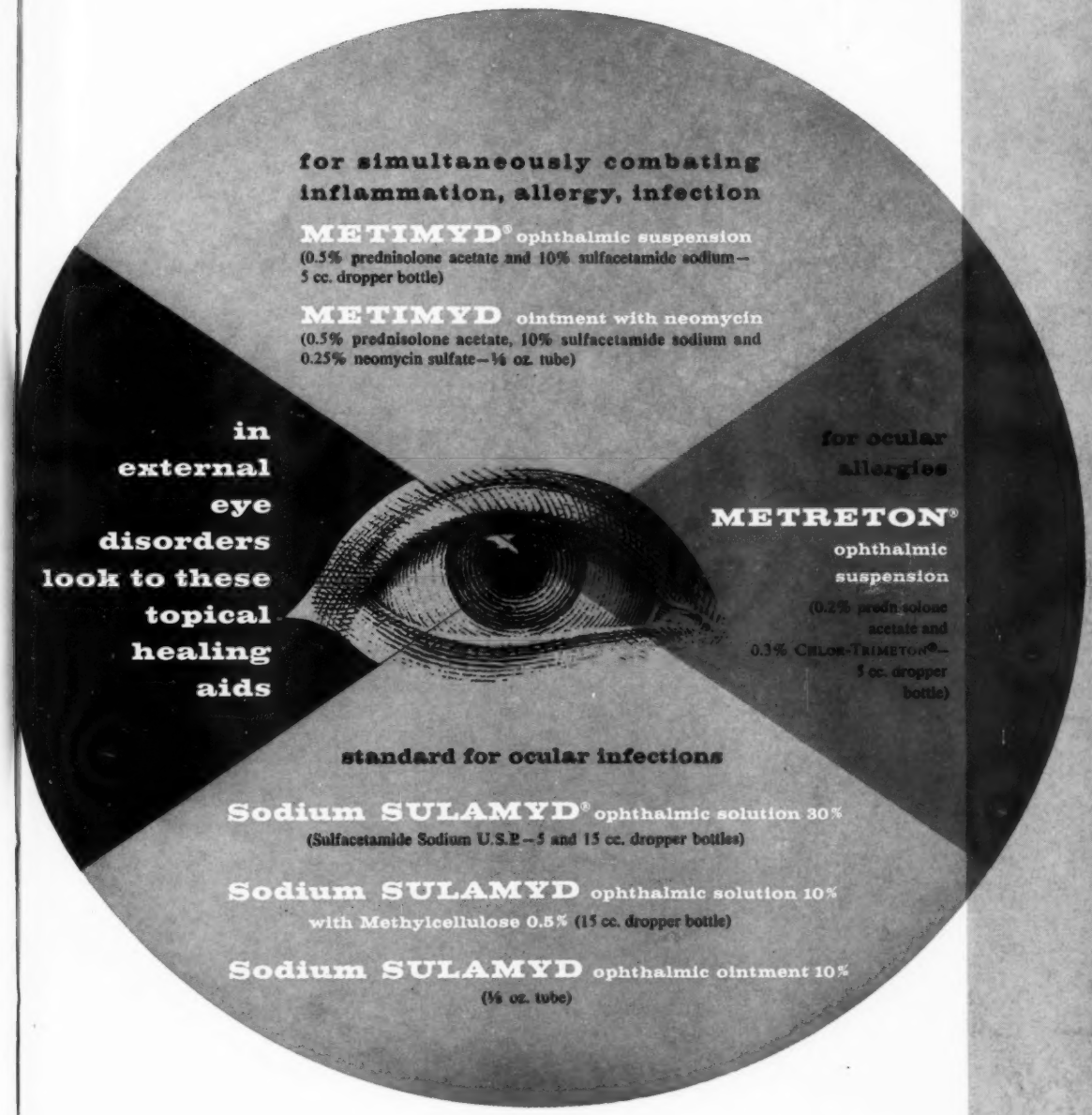
The Medical Assistant. A guidebook for the nurse, secretary and technician in the doctor's office. By Miriam Bredow, Dean of Women, Eastern School for Physicians' Aides, New York. 430 pages, illustrated. 1958, The Blakiston Division, McGraw-Hill Book Company, Inc., New York, Toronto and London. $7.50.

Etiology and Treatment of Leukemia; Proceedings of the First Louisiana Cancer Conference. Edited by Walter J. Burdette, M.D., Professor and Head, Department of Surgery, University of Utah College of Medicine, Salt Lake City. 167 pages, illustrated. 1958, The C. V. Mosby Company, St. Louis. $4.00.

Life Insurance and Medicine; the Prognosis and Underwriting of Disease. Edited by Harry E. Ungerleider, M.D., Director of Medical Research, and Richard S. Gubner, M.D., Associate Director of Medical Research, Equitable Life Assurance Society of the United States, New York. 994 pages. 1958, Charles C Thomas, Springfield, Illinois. $16.50.

Rehabilitation After Illness and Accident. Edited by Thomas M. Ling, M.D., Consultant Psychiatrist to the Marlborough Day Hospital, and the late C. J. S. O'Malley, C.B.E., former Medical Director, Camden Road Rehabilitation Centre, London, England. 119 pages. 1958, The Williams & Wilkins Company, Baltimore. $3.50.

British Medical Bulletin. Causation of Cancer. Symposium, prepared by 27 contributors. Vol. 14. No. 2. 196 pages. 1958, Medical Department, The British Council, London. $4.00.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The Medical Muse

RICHARD ARMOUR

DEAR DEPARTED

It's 10 P.M., and the party
Has just got into full swing,
When, as it so often happens,
The telephone's heard to ring.

The call is, of course, for the doctor,
It's the fourth such night in a row.
He gathers his hat and coat up
And says he is sorry to go.

The ladies continue their yakking,
Untiringly shooting the breeze,
While the men all look at their watches
And envy those lucky M.D.s.

THE WHEEL CHAIR

The wheel chair, when it's self-propelled,
Can go as if bat-out-of-helled,
And with no sound of motor humming
Gives you no warning that it's coming.

On rubber tires, with spinning spokes,
It sneaks up on unwary folks,
On doctors, nurses, friends and foes,
And bashes rears and crushes toes.

Oh, cars and trucks are fierce on highways,
And so are bicycles in byways,
But in a dimly lighted corridor
The swift and silent wheel chair's horrider!

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DORBANTYL® (danthron + dioctyl sodium sulfosuccinate)

PERISTALTIC STIMULANT + FECAL SOFTENER

In cathartic habituation, the action of DORBANTYL diminishes dependence on cathartics as it relieves constipation: "Careful attention to diet and fluid consumption, along with Danthron-D.S.S. [DORBANTYL] resulted in improved colonic motility. As bowel tone increased, gradual withdrawal of medication to complete discontinuance was possible in most instances."*

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*Marks, M. M.: Clin. Med. *4*:151, 1957.

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A monthly service dealing with the basic problems of increasing your net income and building personal capital . . . *in the face of today's high tax structure*

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Postgraduate Medicine

SEPTEMBER 1958

The Toll Taken By Taxes And Inflation - is most felt by the physician. As a self-employed individual, there is comparatively little he can do to tax protect earned income. That earned income is also subject to inflation. No doctor can safely ignore the combined impact of inflation and taxation on his income.

Consider just what has happened over the last 12 years. Assume a young doctor back in 1946 had income of $7,500 a year. He is married and has two children. His real income has not increased at all in terms of purchasing power by 1958 unless it now exceeds $11,000 a year. The difference between $7,500 income and $11,000 income -- an amount of $3,500 -- is actually consumed by the double inroads of taxes and inflation.

The doctor who had income of $25,000 a year back in 1946 has actually lost ground in the battle against taxes and inflation, unless he has been able to increase his annual income by $9,500 to $34,500 a year. The following table shows the total taken by taxes and inflation in the 12-year period between 1946 and the current year.

Doctor's 1946 Income	1958 Equivalent Income	Tax and Inflation Toll
$ 7,500	$ 11,000	$ 3,500
10,000	14,500	4,500
25,000	34,500	9,500
50,000	68,000	18,000
100,000	132,000	32,000

Only One Out Of 13 Americans Retires - in financial independence. Three-fourths of those who have retired from gainful activity currently have income under $1,000 a year. Those are the figures today. In the future, those figures will change. From Social Security alone, the average retired couple will realize close to $2,000 a year tax-free income. Payments from employment pension plans will add to that total. But at the present time, the doctor does not benefit from Social Security coverage or from pension due to an employment plan. If the doctor is to retire to a financially

secure retirement, he will have to provide it himself. To do that, he must plan now.

One noted authority in the planning field, the late Mayo A. Schattuck, pointed out the difficulties faced by the doctor. Unless he inherits property, his income initially is dependent solely upon exchanging his skills and services for compensation. In effect, he is operating a miniature business in which his skills are his product and professional and family expenses are his overhead. Even after a long and arduous training period, at the start of professional practice, his income and his expenses are apt to be nip and tuck. Later, as his income increases, he will be able to set aside some of it for investment. How well he will be able to live at time of retirement will largely depend upon how well he can protect investment of surplus income from taxes and inflation during the saving period.

Your Life Insurance Program Contains A Retirement Feature - When the doctor starts his life insurance program, and when he expands it, he is primarily thinking of security for his widow and children in case of his premature death. But forms of permanent insurance (that is, other than term insurance) also include a savings factor. As the doctor pays premiums, he builds up investment values in his insurance policies -- and that increase in value is not subject to current tax. If the doctor lives until retirement and compelling need for insurance coverage lessens, he can convert the investment values built up in his insurance policies to an annuity for himself and his wife. Unlike most other investments, that conversion from insurance to annuity can be made without tax.

On conversion of insurance policies to an annuity, the annual return paid to the doctor is also tax sheltered. Only payments to him in excess of what is known as the "annuity exclusion" must be reported as taxable income. So life insurance policies do give a large measure of protection against income tax. Such policies are useful and valuable in planning for retirement. But such policies, whether in the form of life insurance or converted annuity, are dollar obligations. They are subject to inroads of inflation. Insurance may furnish an important part of -- but not the complete answer -- to retirement planning.

The Variable Annuity Concept In Retirement Planning - is a new development. It has aroused considerable comment and controversy even amongst insurance companies. Two of the larger insurance companies -- Metropolitan and Prudential -- disagree over its value.

The usual annuity provides for a fixed dollar return at the time of maturity. It has certainty in amount, but if inflation continues that fixed dollar amount may be less than adequate in meeting rising living costs. In general, the variable annuity seeks to protect against

inflation and deflation by providing a varying payment at time of maturity of the annuity. Premiums are invested in part in dollar obligations and in part in equities such as stocks. If at the time of maturity, stock values are up, larger annuity payments will be made. If they are depressed, smaller payments will be made.

Behind the variable annuity concept is the theory that investment in dollar obligations and stocks will protect the annuitant, regardless of whether we are in a period of inflation or deflation when he retires. In a time of inflation, higher stock values promise a higher annuity return to offset increased cost of living. In time of deflation, premiums invested in dollar obligations will yield at least a minimum dollar return. In a deflationary period, that dollar return will go further in meeting one's living expenses, offsetting reduced return from the equity part of the annuity.

* * * *

Providing Your Own Variable Annuity - At the present time, none of the larger established insurance companies issue variable annuity policies. However, one of the major companies is seeking a change in law which would permit it to sell such policies. But some doctors are not waiting for the larger companies to enter this field -- they are setting up their own variable annuities.

The method is simple and involves only consistency in investing surplus funds. With part of the surplus income the doctor pays premiums on annuities bought from an insurance company. Other income left after payment of premiums is invested in sound equities, with emphasis on shares of earnings retention companies. By this method of investing the doctor creates two investment retirement funds. One is in dollar obligations -- the annuity; the other is in equity investments -- the stock fund. In this way the doctor hopes to achieve results similar to that promised by the variable annuity which, as yet, is not generally sold by insurance companies.

A Retirement Pension Created From Professional Income - Dr. Kintner and his associates practised through a medical partnership. They subsequently converted their partnership into a medical association. Thereafter, they established a pension plan for their own benefit (8 doctors) and employes (3 other individuals).

If the pension plan qualified for tax purposes, professional income (otherwise subject to full tax) would yield tax deduction to the extent contributed to the pension plan. Return on contributions to the pension plan would compound tax free. At the time of retirement, a doctor could withdraw his share of the pension plan as capital gain. A court held that when the doctors changed form of professional operation from a partnership to an association, they became employes of their association. That was the famous Kintner decision pre-

viously reported in Postgraduate Medicine. Subsequently, the Internal Revenue Service announced that it would follow the decision.

While the Service promised to issue a detailed ruling explaining how a partnership could be changed to an association so as to qualify the doctors as employes and beneficiaries of a pension plan, that ruling still has not been released. But even in the absence of a detailed ruling, the doctor might well explore, with his attorney, methods of converting a medical partnership into a medical association for pension plan benefits. If the method utilized in the Kintner decision is followed exactly, the Service will not attack. Aside from the income tax advantages offered, there also are estate tax savings.

When the doctor thinks of retirement, he also considers the welfare of his wife. Under the medical association pension plan, if the doctor did not live until retirement, his pension benefits could be distributed to his widow. To the extent such benefits reflect contributions for the doctor by his association, such benefits would not be subject to estate tax regardless of the size of the doctor's estate. The medical association pension plan offers a tax-protected pension for the doctor in retirement. It also means estate tax-free benefits for his widow if he dies prematurely.

* * * *

Are You Taking A European Vacation Trip This Year? - If you are flying back, here's something to consider. Don't overlook bargain buys at one of the "tax-free" airports. At these airports, foreign import taxes are avoided, which means a saving in purchase price. Your purchases will have to be included in your $500 duty-free exemption, but you will be able to bring in more goods within that exemption. For instance, a good Leica camera with lens might cost only $250 at one of these airports. Purchased elsewhere in Europe, price might be almost double.

Where are these tax-free airports? They include: Shannon, in Ireland; Orly Field, in Paris; Kastrup, in Copenhagen; Schipohl, in Amsterdam; and the new Melsbroek, in Brussels.

If Your Child Reached College Age This Fall - you may have been unpleasantly surprised by recent increases in tuition fees. Such educational costs are not tax deductible, so they could consume a considerable amount of your before-tax income. If you currently are in a short cash position, you might consider borrowing to meet education expenses. When you repay principal, you don't get a tax deduction. But interest on that loan is deductible. Many banks offer educational loans. One organization, The Tuition Plan Inc., 347 Fifth Avenue, New York City, offers loans specifically for college tuition purposes. School gets tuition money in lump sum at beginning of academic term. You in turn pay off Tuition Plan in equal monthly installments.

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DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

June 25—In the morning with Justin, studying technics of abstracting, and, at noon, lunch at the Quadrangle Club, meeting Nerlove. At night to dine at the Downtown Club with the Brandeis Associates and heard Max Lerner tell of his travels and his views of our civilization; thereafter in the cocktail bar with Lerner and Lucie Freeman and heard and told merry tales.

June 26—Much scrivening and with Mistress Pepys to call on Minnie Kirsner, who seems well on the road to recovery. So walked some miles with Mistress Pepys, and till late completely engrossed in "The Enemy Camp," by Jerome Weidmann, full of wise philosophy and completely absorbing.

June 27—Reading this day "The Image Makers," by Bernard V. Dryer, which is full of accounts of neurology and plastic surgery beautifully woven into a passionate novel. The accounts of the difficulties in Tangier and Algeria are of the moment.

June 28—To play at golf with Mistress Pepys, the Friedells and Steins and played a little better, but Barbara has improved immensely, which shows what practice will do.

June 29—Reading, writing and resting and saw a doubleheader between the White Sox and Senators on television, and surprised that the eyes do not follow the ball as they do at the stadium.

June 30—At noon came Harold Swanberg to plan for his scholarship fund and for the American Medical Writers' Association. The city overflows with Kiwanians. In the evening with Mistress Pepys and Sam Pearlman, walking along the lake shore in beautiful twilight and discussing at length the changing viewpoints of medicine, welfare and politics; also completed "A Summer Place," by Sloan Wilson, which reveals the tribulations of the children of divorced parents.

July 1—To the Electric Club for lunch with Albert Pick, Mentzer, Remer, the Variety Club and La Rabida auxiliaries, Russ Stewart, Kupcinet and many more to plan a dinner for Bob Hope and funds for rheumatic fever. Old Pepys suggested we call the collection our "Hope chest." Thereafter shopping with Mistress Pepys and purchased a bauble for our anniversary, being now married 44 years, which, considering the disposition and foibles and general meanness of old Pepys, is quite a while. And read two statesmanlike addresses by Francis Brown of Schering and John Connor of Merck, and rejoiced at the type of leadership now prevailing in our great drug industries.

July 2—Reading now a British novel called "The Graver Tribe," by Edward Candy, which deals with the ethics of surgical decisions and the politics of decisions regarding staff appointments under the British National Health Plan. It is informative but told with little artistry and a strange sort of reticence in the love interest that is little short of prudishness.

July 3—To Ravisloe to play at golf with Maurice Goldblatt, who performs well on the tee, and then to dine with the Altheimers and Weiner, newly come from Flint, and played somewhat poorly at gin in a six-handed contest.

July 4—Celebrated the Independence Day without spending any of my time at the desk fulfilling my obligations.

July 5—Again to play at golf, doing a little better with each effort.

July 6—To Highland Park, visiting with the children and the grandchildren and the Lewins and reminisced of the good old days and discussed the stock market with Georgia, aged 14.

July 7—Greeted Mistress Pepys, recognizing this anniversary of 44 years of marriage, and so much has been encompassed that the passage of the time seemed small indeed. At the desk all the day in cooperation with Justin and reading "Surgeon of Fortune," by Welburn Kelley, a medical historical novel of a Scottish surgeon who came to

(Continued on page A-182)

running noses and open stuffed noses orally

Relief in minutes...lasts for hours

In the common cold, nasal allergies, sinusitis, and postnasal drip, one timed-release Triaminic tablet brings welcome relief of symptoms *in minutes*. Running noses stop, clogged noses open—and *stay* open for 6 to 8 hours. The patient can breathe again.

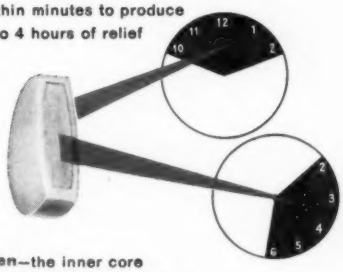
With *topical* decongestants, "unfortunately, the period of decongestion is often followed by a phase of secondary reaction during which the congestion may be equal to, if not greater than, the original condition. . . ."* The patient then must reapply the medication and the vicious cycle is repeated, resulting in local overtreatment, pathological changes in nasal mucosa, and frequently "nose drop addiction."

Triaminic does not cause secondary congestion, eliminates local overtreatment and consequent nasal pathology.

*Morrison, L. F.: Arch. Otolaryng. 59:48-53 (Jan.) 1954.

Each timed-release tablet keeps the nasal passages clear for 6 to 8 hours— provides "around-the-clock" freedom from congestion on just three tablets a day

first—the outer layer dissolves within minutes to produce 3 to 4 hours of relief



then—the inner core disintegrates to give 3 to 4 more hours of relief

Each timed-release TRIAMINIC *Tablet contains:*

Phenylpropanolamine hydrochloride	50 mg.
Pheniramine maleate	25 mg.
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Dosage: 1 tablet in the morning, mid-afternoon, and in the evening, if needed. To be swallowed whole to preserve the timed-release feature.

Also available: Triaminic Juvelets, timed-release, half-dosage tablets; Triaminic Syrup, for children and those adults who prefer a liquid medication.

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America, treated General Washington for an abscess of the buttock, worked in Georgia with the Creek Indians, survived the yellow fever outbreak with Benjamin Rush, and had a love affair so stupid that the reader becomes impatient with him. Read also the reminiscences of the Scottish health officer James Fraser, which is informative and dull. In the evening the family to dine with Barbara Friedell, whose efficiency is a constant marvel to her papa.

July 8—By plane to Boston, arriving in a blast of heat, and drove to Joe Cohen's house in Brookline, where he sat on his piazza clad only in shorts enjoying "The Enemy Camp." Thereafter to Newtonville to dine in the garden with the Haneys until the rains came.

July 9—To visit Dr. Joseph Thimann in the Washingtonian Hospital and observed the technic of the conditioned-reflex treatment of alcoholism, while Mistress Pepys journeyed to observe The Wayside Inn, where Longfellow thought up Paul Revere's ride. Next, motoring to Falmouth and Cape Cod, stopping en route to eat wonderful clam chowder and scallops at The Hobomock in Pembroke Center. In Falmouth to a beautiful cocktail party at the home of the Tildens, meeting Geoffrey Whitney, Faxon, Milford Lawrence and Phil Lyons. Then all to the armory, where some 700 came to dine and be inspired to build the new hospital. So after that for a pleasant night in the gorgeous Nautilus Motor Inn, which looks out on the sea.

July 10—Early to meet the authorities and visit the Oceanographic Institute, observing the intricacies of research on life in the depths. Then with N. Faxon to see the Marine Biologic Laboratory of Woods Hole and here were Szent Gyorgi and his lady, working on muscle physiology, and G. Clowes, who for so long guided Eli Lilly and now concerned with chemotherapy of cancer and a fine library with many periodicals. In the afternoon to dine with the Lyons at the Dome and then to the Falmouth Playhouse at Coonamassett to see Hume Cronyn and Jessica Tandy in two short plays by Sean O'Casey and one by Benn Levy, and enjoyed particularly Cronyn's masterful depiction of the famous Chekhov monologue of Professor Ivan Ivanovitch Nyukhin, who obeys his wife's order to talk about tobacco.

July 11—By the N.Y.N.H. & H.R.R., which finally made up its mind to go, riding to Stamford and from there motoring to Katonah, and then on to Scarsdale for a luxurious party at the Stanley Lasdons'. And en route

finished two fine mysteries by Geoffrey Household, "A Time to Kill" and "A Rough Shoot," and also Cronin's stereotyped newspaper story "The Northern Light." Best of all was Anita Block's "Love Is a Four Letter Word," for her story is realistic, witty and exciting.

July 12—To play at golf with Milton Freiwald, just returned from Russia and Poland and all the tour of the Philadelphia Symphony, and our host Bill Lasdon, and all played pretty well. In the afternoon in happy conversation and at night came Friedman, Richter, Stanley Lasdon and Abrams, who produces the Emerson radio and television.

July 13—A morning of restful relaxation and in the afternoon flying home on the American Captain's Flagship, which is among the best of commercial aviation. En route read "The Contenders," by John Wain, which at first was slow but later gathered pace—a tale of boys who were rivals from boyhood onward for success and love and fame, told softly by one who looked on.

July 14—At the desk, which grows more complex.

July 15—More of the same—and in the afternoon watched the amazing Cubs, no longer full of lassitude.

July 16—At noon to Charles Lawrence for my checkup, which we both enjoyed. Then to the Board of Governors of the Chicago Heart Association, where Wright Adams presided along with DeWitt Clough. Here were Fenn, Katz, Strauss, George Jones, Maurice Goldblatt and many more, and the reports showed great progress, with about $1,200,000 from the annual collection.

July 17—To play at golf with Mistress Pepys, Frank Stern and Dave Scheffler, and pleased with my improvement. Then to dine with the Winstons along with Judge McCormick, Byerrum, Sutton and Eldred and all the ladies, and all the talk was of the trou-

(Continued on page A-184)

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References: W. J. Kolff, "Acute Renal Failure: Causes and Treatment," The Medical Clinics of North America, *30*:1052 (July 1955).

Peter Forsham, "Symposium on Adrenal Corticoid Therapy," Metabolism, 7:19 (Jan. 1958).

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bled Middle East and the racket hearings and the United Nations on television.

July 18—To lunch came Art Snider, talking some hours of the news of medicine. In the evening to dine at Dr. Edmund Jacobson's, with the Kirsners and the Zelzers, with talk of music and humor and particularly of Cliburn and Tebaldi.

July 19—Saw a fine baseball game between the Cubs and Milwaukee on television, at the same time reading "The Old Blood," a sort of study in genetics of Dutch planters in British Guiana by Edgar Mittelhalzer, dealing with problems of slavery and integration and lust. In the evening to see Walter Slezak, a great actor, with somewhat lesser talent in his support, playing "The Little Hut," which his skill made as enjoyable as when I saw Robert Morley play it in London.

July 20—At noon to Ravisloe to play at golf, still wasting shots unnecessarily. A golfer in Florida asked his somewhat elderly caddie, "What does the usual golfer score around here?" The answer: "Well, most of them tries to make as few as they can, but they generally takes some more!"

July 21—Justin and Anne's seventh anniversary, so took them to the Pump Room, where almost anything but scrambled eggs comes out on a flaming torch. And saw Pat Hoy, so young and handsome one could hardly recognize him. Read also "The Narrow Search," a tale of kidnaping and the finding of the child hidden on a boat on the British canals.

July 22—Early awake, being now 69 years old, and overjoyed with the messages which came from near and far; at noon to speak on "Medical Progress" at the Chicago Rotary Club, where all sang "Happy Birthday." Here were some 800 Rotarians and among them Clough, Egdorf, Goodman, Huber and Hutton. Next to play at golf with Maurice Goldblatt, who keeps improving. Thereafter came some 60 friends to delight in a wonderful feast that Mistress Pepys designed beautifully and more singing and telling of tales and playing games. And, the hour being late, kissed all the ladies young and old a fond good night—and so to bed.

July 23—At the desk reading Riseman's "Electrocardiogram Clinics," which Holt Seale sent me, and thought it wonderfully designed to help the beginner in this art; also read Hollender's "The Psychology of Medical Practice," which is unique in conveying innumerable hints on how to act with patients and what to say in the tough times.

This day came a memento of my visit to the Woods Hole Oceanographic Institutions. While there old Pepys told this story.

> A visitor from earth arriving on the moon observed that all the damsels were beautiful, having the countenance of Sophia Loren, the contours of Brigitte Bardot, and the locomotive equipment of Marilyn Monroe. When he inquired, a guide took him to a long building where an assembly chain was constructing the damsels all of the same mold. "We do nothing on earth like this," said the visitor. "What do you do?" asked the moon guide. When the visitor explained the biologic phenomena involved, the moon guide laughed sarcastically. "Why the merriment?" inquired the visitor. "That," said the moon guide, "is the way we make automobiles."

So Harry J. Turner, Jr., marine biologist, wrote to old Pepys:

> As a result of your enlightening discussion of the reproductive physiology of the lunar automobile held in room 306, WHOI (the wet lab), my colleagues have asked me to request you to supply reprints of the

(Continued on page A-188)

Jest for Today

The wealthy but somewhat aged bachelor enlisted the services of a marriage broker—a shadchen, that is—to find him a wealthy widow who should also be a doll. The shadchen called in great excitement, "I got for you just the one," he said. "She looks like a picture."

So a meeting was arranged for dinner at Lindy's.

The bachelor winced when he spotted the damsel seated in a booth. Her ears protruded, her nose was like a bent fender, and her hair fell in disorder over thick shaggy eyebrows. To the shadchen he said: "This you call a picture?"

The shadchen shrugged: "Either you like Picasso or you don't," he said.

* * *

She was at a meeting of the American Psychoanalytic Association. As the room darkened and the speaker started to show his slides, she felt a gentle pinch on her thigh. She shifted restlessly and looked at her neighbor threateningly. A few minutes later she felt a harder and more intimate pinching. She decided to move her seat. Then she changed her mind. "After all," she said to herself, "why should I get angry? That's *his* problem!"

* * *

You Tell 'Em
THE NEWEST SCRABBLE

Three men rent a hotel room; each brings a quart of "Seven Crown." They sit and drink for one hour, then one of them gets up and leaves. The other two have to guess which one left.

* * *

Paper Work

A Midwesterner was in a New York taxi. The cabby wheeled wildly in and out of traffic. Suddenly a pedestrian stepped off the curb against the light and the cabby slammed on the brakes. Figuring that such unusual courtesy called for an explanation, he turned around and said: "If you hit 'em, you gotta fill out a report."

* * *

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Average FURADANTIN dosage in prostatitis—Acute cases: 100 mg. q.i.d. until cured. Chronic cases: 100 mg. q.i.d. for 10 to 14 days; depending on response, dosage may then be reduced to 100 or 200 mg. daily for 1 to 3 months.

Supplied: Tablets, 50 and 100 mg., bottles of 25 and 100. Oral Suspension, 25 mg. per 5 cc. tsp., bottle of 60 cc. Intravenous Solution, sterile 10 cc. ampules (60 mg. FURADANTIN each) box of 12.

References: 1. Alyea, E. P.: Infections and Inflammations of the Male Genital Tract, in Campbell, M.: Urology, Philadelphia, W. B. Saunders Co., 1954, vol. 1, p. 643. 2. Carroll, G., in panel discussion, J. Am. Geriat. Soc. 5:635, 1957. 3. Barnes, R. W.: Prostatitis, in Conn, F.: Current Therapy 1957, Philadelphia, W. B. Saunders Co., 1957, p. 353. 4. Barnes, R. W., in discussion of Chinn, J., and Bischoff, A. J.: Tr. West. Sect. Am. Urol. Ass. 22:189, 1955.

NITROFURANS—a new class of antimicrobials—neither antibiotics nor sulfonamides

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FURADANTIN

following articles that have appeared in *Excerpta Medica,* Section Artifacta de Luna 66:77-88 (January 1) 2058:

1. Insemination, fertilization and early cleavage of the ovum of the lunar self-propelling vehicle.

2. A comparative study of the early embryology of the lunar Cadillac and the Model Z Ford.

3. The incidence of embryonic amputation in the lunar automobile with special reference to the left rear hubcap.

4. Evidence of sex-linked inheritance of the chronic radiator base drip in the lunar Lincoln.

What my boys most want to know is the exact location of the lunar damsel-type female assembly plant—but I think they will do better work if they keep down to earth.

So old Pepys replied:

The questions which are proposed by your associates have greatly stimulated our conference of new research facilities. I am now endeavoring to raise funds to establish an expedition with a view to determining definitely the location of the lunar damsel-assembling plant. If the project should prove successful, we propose to incorporate an agency to provide low-cost tours which I think would appeal to your associates.

July 24—To Charles Lawrence and then to J. Sammet for the necessary measures involved in determining the end results of the operative procedure for polyps 18 months ago. And all the views—direct and by roentgen ray—revealed complete absence of any more. Thereafter resting and viewing the White Sox toppling before 19 year old pitcher Pappas.

July 25—Early came Dr. Arthur Bernstein to consult about a biography of Dr. Frederick Tice, which he is preparing. Thereafter came William I. to tell of his literary activities. Reading also "The Violated," by Bourjaily, which tells the lives of three men and a girl, full of violence, sex and a sense of living with no purpose. At night to Sportsman's Park, and much disappointed by the performances of the trotters and pacers, but as my brother Albert remarked, "You can enjoy the fresh air."

CURRENT COMMENT

Dr. Brian Ackner, London: "It is not valid to attempt to measure anxiety by using objective measures of bodily change."

* * *

Dr. G. Pampliglione, London: "Nowadays, emotion is considered an agitation of the mind, involving somehow the brain."

* * *

Dr. Peter Sainsbury, Chichester: "It would be consistent with our findings, with the reports of the majority of our patients, and with what we found to be the practice of the majority of psychiatrists, if the term tension were limited to the muscular manifestations of the emotion."

* * *

NO TEETH OR SCURVY

"Lady Mellanby, Mr. P. J. Holloway and Mr. R. J. C. Stewart investigated the effect on the enamel of teeth of 20 proprietary brands of fruit squashes and cordials, various aerated drinks, fresh fruit juices, acid drop sweets and iced lollipops. All, they found, caused erosion. . . . Aerated drinks were not as erosive as fruit squashes."

From the *London Times*

Write your own conclusions!

* * *

NOTHING LIKE A DAY OFF

"Seventy-five per cent of hospital outpatients should be seen by the doctor within half an hour. Most of them should be seen in 10 to 15 minutes. These are the waiting-time limits which the Ministry of Health wants hospitals to achieve. At present, complaints of waits of one or two hours are not uncommon."

From the *London Times*

* * *

See no evil, speak no evil, hear no evil—and you might as well stay home from all parties.

* * *

July 26—A hot and humid day, so watched television baseball and read a terrific story of the Sino-Japanese War and World War II. In this story, "The Time of the Dragons," Alice Ekert-Rotholz describes 30 years of intrigue, terror and passion in Shanghai and Thailand. In 1939 the author went with her husband Dr. Rotholz to Bangkok, where he practiced in the British dispensary for 12 years. Now they live in Hamburg. In the evening to dine at Ravisloe.

July 27—All this day at the desk and reading "The Evil Eye," by Edward S. Gifford, Jr., M.D. Here one can learn not only how to hex the enemy but also the protective measures. Especially fascinating is the chapter on "Sexual behavior and the eye." Here is a reference to "bedroom eyes" and some fine references to the general literature. In the evening to the gorgeous wedding at the Drake of Mike Rosenberg and Madeline Pelts-Wolfsohn, with thousands of floral decorations and delightful pageantry and champagne, music and dancing. So here were Dan Ryan, McFetrich, Russ Stewart, the Hoffmans, Kaplans and hundreds of the city's most prominent to wish long life and happiness to the newlyweds.

July 28—At the scrivening and by the afternoon plane to New York reading en route the *Journal of the American Medical Association, British Medical Journal, Lancet, Reader's Digest* and *Abstracts of Soviet Medicine,* being astonished to discover in the last named several reports of epidemics of diphtheria with a high rate in Moscow and much tuberculous meningitis; 540 children recorded had scarlet fever twice and 16 had it three times.